Neurotransmitters doing double duty as gene regulators and tumor-microenvironment signals

A recent collaborative paper digs into disease mechanisms across human tumor multi-omics studies, epigenetics, and brain physiology in effort to understand interactions between tumor and the healthy brain.

Interactions between tumor and the surrounding health tissue is becoming an important question, particularly in the brain. As Hsiao-Chi (Eileen) Chen, graduate student with Baylor College of Medicine explained, “We're trying to understand tumor microenvironment which is very different from other types of cancer because in brain tumor, there's a lot of different cells like neurons or glial cells and neurotransmitters that's very different from other locations in the body.”

Ependymoma is a devastating tumor type arising from cells lining the ventricular system of the brain and spinal cord. Both adults and children with this cancer type often develop epilepsy. “You can imagine if you have something in the brain messing around with the environment you will definitely trigger a seizure event. So here we are wondering if it's manipulating the neural activity. And also, how does that tumor affect environment to benefit their growth?”

Chen is the lead author of “Histone serotonylation regulates ependymoma tumorigenesis” recently published in Nature to address this question. This work highlights the combined efforts of the laboratories of CENOS-member Steven Mack at St. Jude Children Research Hospital and Benjamin Deneen at Baylor College of Medine.

Past studies in adult glioma demonstrated elevated neuronal activity increased tumor growth. It turns out to be more complicated, where the type of neurons and brain regions involved can determine tumor responses. Eileen said they focused on serotonin, a neurotransmitter with diverse roles including mood regulation, body states, and learning and memory, because high levels of the transporter on the surface of tumor cells.

“So then we are wondering why would the tumor cells want to import the serotonin into the cell? We started to touch on epigenetic regulation because in the in some previous studies, we found that histone, this molecule which wraps the DNA, can modified by adding the serotonin to it. This is very, very cool because before 2019, it was only known that the histone can be chemically modified by smaller chemical group.”

But serotonin is a neurotransmitter. It is surprising to find neurotransmitters acting directly on histones to affect expression of downstream genes. However, histone serotonylation, when the serotonin is added directly to the histone to change its properties, has recently been found to regulate gene expression to direct changes in brain activity in different cell types and developmental processes. This study identifies histone serotonylation may also have important roles in a disease context.

What kind of the genes are being regulated by histone serotonylation? This ties into long term research interests of Dr. Mack, where numerous candidate developmental transcription factors have been identified in ependymoma. Investigators then implemented an in vivo screening technique developed by Dr. Deneen’s group to identify the responsible transcription factor and found ETV5, which regulates the formation of glial cells.

“So then we ask how does it affect the tumor and found that if you put more ETV5 into the tumor, the tumor will grow faster. Remove it from the tumor, growth decreases. [We want] to understand the molecular mechanisms related to it … and we found this very unique observation that when we overexpressed ETV5 in the tumor, we found there are more genes being downregulated.”

Researchers identified neuropeptide Y (NPY), a widespread neurotransmitter with diverse physiological functions spanning immune cell regulation and brain activity modulation, was downregulated by ETV5. Further, overexpressing neuropeptide Y caused the tumor to grow slower with several genes related to synaptic transmission being downregulated.

“Then we started to wonder if NPY was regulating brain activity after we overexpress neuropeptide Y. So we studied electrophysiology in studies led by [a postdoc Ben’s lab]. We found that this mouse model we're using can recapitulate the clinical symptoms of the patients that these mice were capable of seizures. When we overexpress neuropeptide Y, you suppress this event and also the brain hyper excitability of the mice.”

“So I feel there is are potential clinical applications from this study, including like how you change the serotonin level and NPY in the environment to slow down the brain activity.”

Identifying how to use these findings clinically is complicated by the fact that both serotonin and NPY has several different effects as a neurotransmitter with diverse receptors effecting the function and development brain in diverse ways. Chen states that developing new tools and future studies of these mechanism will the key to untangling the complexity of interactions between tumor and micro-environment.

The paper “Histone serotonylation regulates ependymoma tumorigenesis” can be accessed at https://www.nature.com/articles/s41586-024-07751-z

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