Aggressive Growth of Common Brain Tumors Linked to Single Gene

Finding could facilitate more effective therapies for dangerous subset of meningiomas

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UC San Francisco scientists have uncovered a common genetic driver of aggressive meningiomas, which could help clinicians detect such dangerous cancers earlier and lead to new therapies aimed at curing these difficult-to-treat tumors.

Meningiomas are tumors that grow from the layer of tissue that surrounds the brain and spinal cord and are the most common central nervous system tumor in the United States. Although the vast majority are benign and grow slowly, over time they can lead to headaches, seizures, neurological deficits and even death.

Most meningiomas are treatable with radiation therapy or surgery. However, approximately twenty percent of meningiomas are aggressive and can recur even after surgery and radiation therapy. In the new study, published online March 27, 2018, in Cell Reports, a team led by UCSF's David Raleigh, MD, PhD, found that increased activity of a gene known as FOXM1 appears to be responsible for the aggressive growth and frequent recurrence of these tumors.

Raleigh, an assistant professor of radiation oncology and of neurological surgery and member of the UCSF Helen Diller Family Comprehensive Cancer Center, hopes the finding will be an important step towards correctly diagnosing these more aggressive tumors: "There haven't been as many studies on what drives 'problem' meningiomas," he said. "For clinicians, patients, and families, these are the most heartbreaking cases because we expect to cure meningiomas, but sometimes we can't and we don't always do a good job of differentiating 'good' and 'bad' meningiomas ahead of time."

In order to investigate what might be driving aggressive meningioma, Raleigh's group examined 280 human meningioma samples collected by Michael McDermott, MD, and other faculty members in the Department of Neurological Surgery at UCSF between 1990 and 2015. Using an array of techniques, including RNA sequencing and targeted gene expression profiling, the researchers searched for links between gene activity and protein production in these tumors and the clinical outcomes of patients.

Raleigh's team found that a gene named FOXM1 was at the heart of aggressive meningioma

growth, and a signpost of subsequently poor clinical outcomes, including death. Previous studies have implicated FOXM1, which encodes a transcription factor protein capable of regulating the activity of many other genes, in many other human cancers, including liver, breast, lung, prostate, colon, and pancreatic cancers.

In the new study, the researchers found that heightened FOXM1 activity was the unifying factor between aggressive meningiomas in both men and women, in older and younger patients, and in meningiomas arising in different parts of the brain. Not only did the gene's activation seem to underlie newly diagnosed tumors, but it was also an important driver of tumor recurrence following treatment.

The researchers also identified new links between aggressive meningioma proliferation and activation of an intercellular signaling pathway called Wnt — which typically plays a role during embryonic development and tissue formation. Given that the protein produced by FOXM1 is known to transmit signals along the Wnt pathway, the new data suggests that FOXM1 and the Wnt pathway working in concert may drive subsequent meningioma proliferation.

Raleigh's group also looked at DNA methylation — chemical modifications of the genomic material that affects whether or not specific genes are expressed in a given cell. Previous research has identified excessive methylation of DNA, or "hypermethylation," as a ubiquitous aspect of cancer development. The new study found significant hypermethylation in the most aggressive meningiomas, and showed that these DNA modifications specifically silenced genes that usually inhibit FOXM1 expression and Wnt signaling. Together, these findings suggest that hypermethylation may be an early trigger that leads to the development of aggressive forms of meningioma.

But according to Raleigh, future treatments will need to have more refined in their actions than simply blocking FOXM1. Though blocking FOXM1 could halt aggressive meningioma growth, the gene's role in regulating a host of other genes suggests that there would likely be significant "off-target" side effects. "We now need to find out what other genes FOXM1 is activating to drive meningioma growth, and block those targets with clinical therapies," Raleigh said.

These new insights may prove particularly beneficial for older patients that have aggressive meningiomas, because elderly patients have more trouble tolerating the cranial surgeries or recurrent radiation therapies that are currently used to control aggressive tumors.

"Aggressive meningiomas are very insidious tumors. They keep coming back year after year. Sometimes, patients get worn down from the treatments, or become so old they can't tolerate them anymore," Raleigh said. "Often, we run out of time, but with our new molecular insights into meningioma biology we may be able to find new cures for these tumors with fewer side effects and better outcomes."

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