Our modeling of FOXM1's role is outlined in the document affixed to this article.

The epigenetic signaling molecule applies universally to endocytosis that transports cell-surface activity into the cytoplasm.

Moving beyond meningiomas and other cancers (e.g. TNBC) disruption of autophagy attributable to mutation of the endocytosis mechanism, bioinformatic search will also link FOXM1 to plaques formation in AD and PD as well as a plethora of other chronic diseases.

Summary

FOXM1 is a crucial signaling mechanism for effective transfer of epigenetic signaling for the surface of cells into the cytoplasm where the cellular defense mechanism of autophagy takes place.

https://medicalxpress.com/news/2018-03-aggressive-growth-common-brain-tumors.html

Aggressive growth of common brain tumors linked to single gene

March 28, 2018 by Aylin Woodward, University of California, San Francisco

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, Ph.D., 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."

Explore further: Imaging features predict tumor grade
More information: Harish N. Vasudevan et al. Comprehensive Molecular Profiling Identifies FOXM1 as a Key Transcription Factor for Meningioma Proliferation, *Cell Reports* (2018). **DOI: 10.1016/j.celrep.2018.03.013**

Journal reference: Cell Reports

MCFIP-Our modeling of FOXM1 provides strong and near certain evidence that this signaling molecule and its three forms are the three glutathione peroxidases (zinc finger, selenium dependent protein kinase signaling molecules) responsible for the critical autophagosome mechanism that supports autophagy.

When the specific step-by-step process for autophagy is understood, without the mechanism for lysosome encapsulation of the different forms of debris caused by apoptosis, the specific signaling molecules for degrading lipids (lipoproteins), carbohydrates (glycoproteins) and proteins cannot take place. FOXM1 is one of the three signaling molecules that activate the lysosome encapsulation. As mentioned previously, it is noteworthy that there are three forms of FOXM1; A, B and C. Inhibition any of these three forms would explain why the substance is prevalent in so many cancers.

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Research Gives Hope to Detecting Cancer in Early Stages

ScienceDaily (Mar. 27, 2012) — Research from Queen Mary, University of London has uncovered the mechanism which causes normal cells to develop into cancer, giving hope in the fight against one of the UK's biggest killers.

The study, published in the online journal *PLoS ONE* on March 26, investigated the role of the notorious cancer gene FOXM1.

Lead investigator Dr Muy-Teck Teh from Queen Mary, University of London, said the team found that the FOXM1 gene "brain washes" normal cells so they adopt a 'memory' pattern similar to cancer cells.

"This research has important clinical implications for early cancer diagnosis, prevention and treatment.

"We knew the FOXM1 gene is present in almost all different types of human cancers so we wanted to understand how excessive levels of it cause normal cells to become cancer-like."

Dr Teh's team used a gene-chip microarray technology to investigate the DNA 'memory' patterns in cells.

Normal cells inherit specific instructions or 'memory' patterns by masking and unmasking parts of their DNA. Maintaining the correct memory patterns is important for normal cell function -- disturbing the memory pattern can lead to cancer formation.

"We knew that excess expression of FOXM1 can lead to cancer but its underlying mechanism was not clear," Dr Teh explained.

"We looked at normal human mouth cells and introduced high levels of FOXM1. The normal cells changed to adopt a memory pattern similar to those in mouth cancer cells and we identified a number of key pattern changes that may be responsible for initiating cancer formation.

"These pattern changes may lead to the identification of biomarkers which could be developed into new diagnostic tests. We are currently working towards developing a practical diagnostic test for detecting mouth cancer at very early stages."

The team's research, funded by the Wellcome Trust and the Facial Surgery Research Foundation, Saving Faces, means that it will be easier to detect changes in cells before they develop into cancer.

Consultant oral and maxillofacial surgeon Professor Iain Hutchison, founder of Saving Faces and co-author on the study, said: "We are excited about this finding as it means that we can now detect changes in cells way before they become cancer cells.

"Mouth cancer, if detected early when the disease is most receptive to surgical treatment, has a very high cure rate. Understanding how a gene such as FOXM1 can convert normal cells into cancer is an important step towards finding new diagnostic tests for early cancer detection."

This study builds on previous studies Dr Teh and his team has done on FOXM1. Published in 2009, Dr Teh found that nicotine could activate FOXM1 and that excessive levels could cause normal human mouth cells to develop into cancer. His research on FOXM1 was awarded 'Molecule of the Year 2010' by the International Society for Molecular and Cell Biology and Biotechnology Protocols and Research for its pivotal role in cancer stem-cell biology.