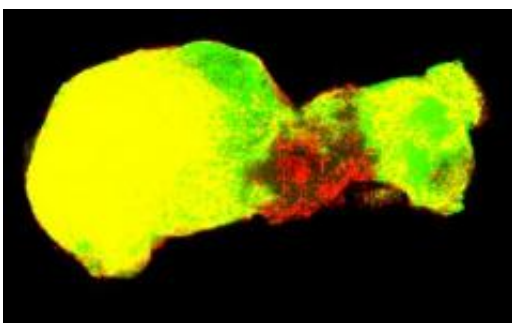


Glioma subtypes determine how the dangerous tumors spread, evade anti-angiogenic treatment

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Tumorous glial cells, labeled in green, have overtaken most of an adult fly brain. Glial cell nuclei are shown in red. Credit: Courtesy of Dr. Renee Read, Salk Institute for Biological Studies

A multi-institutional research team has identified a new mechanism by which the dangerous brain tumors called gliomas develop resistance to anti-angiogenic treatment. The team's report, published online in *Cancer Cell*, describes finding how different molecular subtypes of glioma cells use different strategies to spread through the brain and how anti-angiogenic treatment selects for a treatment-resistant cellular subtype.

"Despite massive basic and clinical research efforts, the [treatment](#) of glioblastoma and other [malignant gliomas](#) remains one of the most challenging tasks in clinical oncology," says Rakesh Jain, PhD, director

of the Edwin L. Steele Laboratories for Tumor Biology in the Massachusetts General Hospital (MGH) Department of Radiation Oncology and co-senior author of the report. "Glioblastomas are highly vascularized and interact closely with pre-existing blood vessels for oxygen and nutrients. They also contain a very diverse population of cells, with characteristics of stem cell and other cells found within the [brain](#), and may use different strategies to recruit or access blood vessels, depending on the local microenvironment and on treatments that are applied."

Previous studies have revealed several ways that gliomas can migrate within the brain - including "co-option" in which [single cells](#) migrate along blood vessels or as dense clusters that lead to the formation of new blood vessels. To investigate mechanisms underlying these two strategies, the research team, primarily comprised of investigators from MGH and the University of California San Francisco (USCF), focused on a protein called Olig2, normally involved in the development of [brain cells](#) called oligodendrocytes and expressed in most glioma subtypes.

Oligodendrocyte precursors (OPCs) that express Olig2 can act as glioma progenitors; and within OPCs, signaling controlled by a protein called Wnt7 is known to play a role in embryonic vascular development within the brain, including the cells' migration along blood vessels. The team's series of experiments revealed the following:

- Olig2-positive glioma cells invade brain tissue by single-cell co-option without affecting the existing vasculature. Increased Wnt7 expression within those cells was required for that strategy.
- Olig2-negative cells grow as clusters around blood vessels - which show increased size and density - and express high levels of the angiogenic factor VEGF. Olig2-negative gliomas exhibit a breakdown in the [blood](#) brain barrier and increased activation of innate immune cells, leading to neuroinflammation.

- In a mouse model of Olig2-positive gliomas that express Wnt7, treatment with drugs that inhibit Wnt or another protein in the Wnt pathway induced glioma cells to lose contact with [blood vessels](#) and form the sort of clusters usually seen in Olig2-negative gliomas.
- In mice implanted with Olig2-positive, Wnt7-expressing cells from human gliomas, treatment of late-stage tumors with a Wnt inhibitor and the chemotherapy drug temozolomide improved survival compared with temozolomide alone.
- Treatment of [glioma](#) cell lines with the VEGF inhibitor bevacizumab promoted single-cell, vascular co-option, most likely by increasing Olig2 expression. Analysis of bevacizumab-resistant cells - including paired samples from human patients taken before and after bevacizumab treatment - supported the conclusion is that anti-VEGF treatment selected for the Olig2-positive, Wnt-expressing [cells](#) that use that vascular strategy.

"We have discovered how Wnt signaling drives the process of single-cell, vascular co-option in gliomas, a mechanism that is strongly induced by anti-angiogenic treatment," says Jain, the Cook Professor of Radiation Oncology (Tumor Biology) at Harvard Medical School.

More information: Amelie Griveau et al, A Glial Signature and Wnt7 Signaling Regulate Glioma-Vascular Interactions and Tumor Microenvironment, *Cancer Cell* (2018). [DOI: 10.1016/j.ccell.2018.03.020](#)

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