Better treatment for brain cancer revealed by new molecular insights

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Nearly a third of adults with the most common type of brain cancer develop recurrent, invasive tumors after being treated with a drug called bevacizumab. The molecular underpinnings behind these detrimental effects have now been published in the July issue of *Cancer Cell*. The findings reveal a new treatment strategy that could reduce tumor invasiveness and improve survival in these drug-resistant patients.

"Understanding how and why these tumors adopt this invasive behavior is critical to being able to prevent this recurrence pattern and maximizing the benefits of bevacizumab," says study author Kan Lu of the University of California, San Francisco (UCSF).

Glioblastoma multiforme (GBM) is the most aggressive type of tumor originating in the brain. GBM tumors express high levels of vascular endothelial growth factor (VEGF), a protein that promotes the growth of new blood vessels that provide nutrients that allow tumors to expand. In 2009, the Food and Drug Administration approved bevacizumab, a VEGF inhibitor, for GBM patients who don't respond to first-line therapies. Although the drug is initially effective, up to 30% of patients develop tumors that infiltrate deep into the brain, making surgery and treatment difficult.

To study how bevacizumab can lead to adverse effects, senior study author Gabriele Bergers of UCSF and her collaborators focused on hepatocyte growth factor (HGF), a protein that controls the growth and movement of cells, because they previously found a link between VEGF

and HGF in GBM cells. In the new study, they found that VEGF inhibits the migration of GBM cells by decreasing HGF signaling through its receptor MET. Moreover, tumors were much less invasive—and survival improved—in mice with GBM tumors lacking both VEGF and MET rather than just VEGF alone. The results suggest that MET plays a critical role in GBM invasion when VEGF is blocked.

"These findings provide a rationale for therapeutically combining VEGF and MET inhibition so that patients can benefit from bevacizumab without developing more invasive tumors," Lu says. Because the VEGF and HGF/MET signaling pathways are active in a variety of tumors, this combined treatment strategy may also be applied to other types of cancer.

More information: Lu et al.: "VEGF Inhibits Tumor Cell Invasion and Mesenchymal Transition through a MET/VEGFR2 Complex." *Cancer Cell*. dx.doi.org/10.1016/j.ccr.2012.05.037

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