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New brain cancer drug targets revealed

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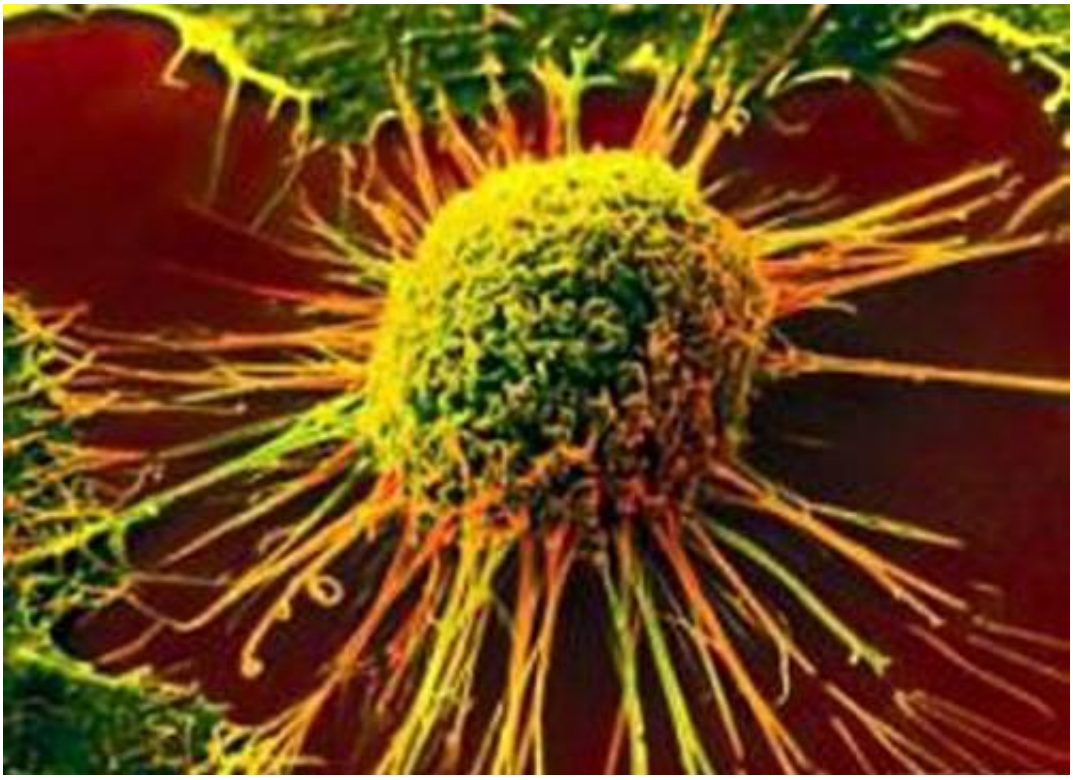

Researchers from Case Western Reserve University School of Medicine and The Cleveland Clinic designed a way to screen brain tumor cells and identify potential drug targets missed by other methods. The team successfully used their technique to find a glioblastoma cancer gene that, when blocked, extends mouse survival rates.

In a study published in *Nature*, the team implanted patient-derived

glioblastoma cells in mice and measured gene activity in the growing brain tumors. They compared the gene activity to that of cancer cells grown in vitro—inside laboratory dishes. The researchers found 55 genes required for the cells to grow inside working brains—in vivo—but not inside laboratory dishes.

"The genes needed for cancer cells to survive in a tumor were not necessarily the same ones needed to survive in a Petri dish," said Tyler Miller, PhD, first author on the study and medical student in the CWRU Medical Science Training Program and Cleveland Clinic Lerner Research Institute. "This means the field may have been missing a whole host of potential therapeutic targets that may actually improve patient outcomes and prolong survival." Glioblastoma is associated with a 2-3 year survival rate and few meaningful treatment options, according to the American Brain Tumor Association.

The high-throughput screening technique revealed new vulnerabilities in glioblastoma tumors that could be targeted by drug developers. Of the 55 genes identified, 12 were all related to a single process—how cancer cells respond to stress. The researchers blocked one of the stress genes in the implanted tumors and the mice lived longer. But blocking the gene inside laboratory dishes did not alter glioblastoma cell growth or survival.

Said Miller, "Our study found that in a natural environment, tumor cells are more susceptible to inhibition of their stress response mechanisms. Current chemotherapies all target proliferating, or dividing cells. That doesn't always work for glioblastoma. Our findings suggest that targeting the stress response may be better at slowing tumor growth than targeting cell proliferation, which opens up a new avenue for therapeutic development."

The two senior authors on the study are Miller's advisors, Jeremy Rich,

MD of the Cleveland Clinic Lerner Research Institute, and Paul Tesar, PhD, Dr. Donald and Ruth Weber Goodman Professor of Innovative Therapeutics and Associate Professor of Genetics and Genome Sciences at Case Western Reserve University School of Medicine. Tesar is also a member of the Case Comprehensive Cancer Center.

According to the researchers, their approach could be used to screen other types of cancers for potential therapeutic targets. Said Miller, "Prior attempts at discovering therapeutic targets have generally been done in cell culture, that is, patient cells on plastic dishes in artificial media to help them grow. Systems like ours that more closely mimic the natural tumor environment are more likely to translate into better therapies for patients."

More information: Tyler E. Miller et al, Transcription elongation factors represent in vivo cancer dependencies in glioblastoma, *Nature* (2017). DOI: 10.1038/nature23000

Provided by Case Western Reserve University