Researchers target specific protein associated with poor survival and treatment

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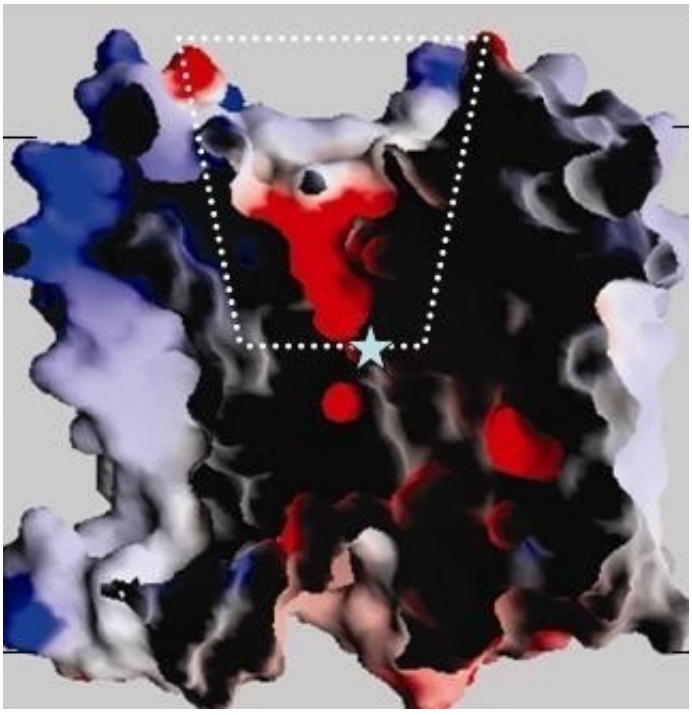

Glioblastoma multiforme (GBM) is a highly aggressive brain tumor with low survival rates, with newly diagnosed patients surviving a median of 14 months and recurrent patients surviving a median of only 3 to 9 months. New therapeutic targets and biomarkers for prognosis are urgently needed. Moffitt Cancer Center researchers recently reported that expression of the protein BIRC3 is associated with poor survival and

recurrent disease in GBM patients; and therefore may be a good therapeutic target.

The standard treatment options for GBM are temozolomide chemotherapy and radiation. These treatment options are effective for a short period of time; however, eventually patients experience tumor recurrence.

One mechanism by which tumors recur and escape anti-cancer treatment is by evading cell death and increasing expression of proteins that inhibit cell death. The Inhibitor of Apoptosis Proteins (IAPs) is a family of proteins that are overexpressed in GBM and prevent cell death; however, it is unknown how the IAP family contributes to GBM treatment outcomes and recurrence.

The Moffitt researchers analyzed IAP gene expression data from 524 GBM patient samples. They found that BIRC3 was the only IAP whose expression was correlated with overall survival in GBM patients. Patients who had high expression of BIRC3 had a significantly shorter overall survival than patients who had low expression of BIRC3. They confirmed this association in a second dataset of 153 GBM patients. Additionally, they reported that BIRC3 expression was significantly higher in patients with recurrent disease than patients with newly diagnosed GBM.

These observations suggest that GBM cells increase levels of BIRC3 in response to treatment in order to survive. They confirmed this hypothesis by showing that the standard GBM therapies temozolomide and radiation cause BIRC3 expression levels to increase. GBM cells that overexpress BIRC3 were resistant to temozolomide and radiation treatment and had significantly lower levels of cell death in a mouse model of GBM following temozolomide treatment.

Analyzing changes in BIRC3 tissue levels in GBM patients could help in determining patient responses to therapy, including long-term prognosis, and may allow resistance to standard therapy to be detected earlier.

"BIRC3 could serve as a biomarker whose expression can be closely followed as patients progress through standard GBM therapy to ascertain if standard treatment is beneficial or not. This could be very advantageous because treatment resistance could be detected earlier since gene expression changes occur well in advance of MRI findings," said senior study author Arnold B. Etame, M.D., Ph.D., assistant member of the Neuro-Oncology Program at Moffitt.

Additionally, BIRC3's role in preventing cell death suggests that it is a viable target for anti-cancer therapies that could be combined with standard treatment regimens in GBM.

More information: Dapeng Wang et al. BIRC3 is a novel driver of therapeutic resistance in Glioblastoma, *Scientific Reports* (2016). DOI: 10.1038/srep21710

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