Brain cancer: Two essential amino acids might hold key to better outcomes

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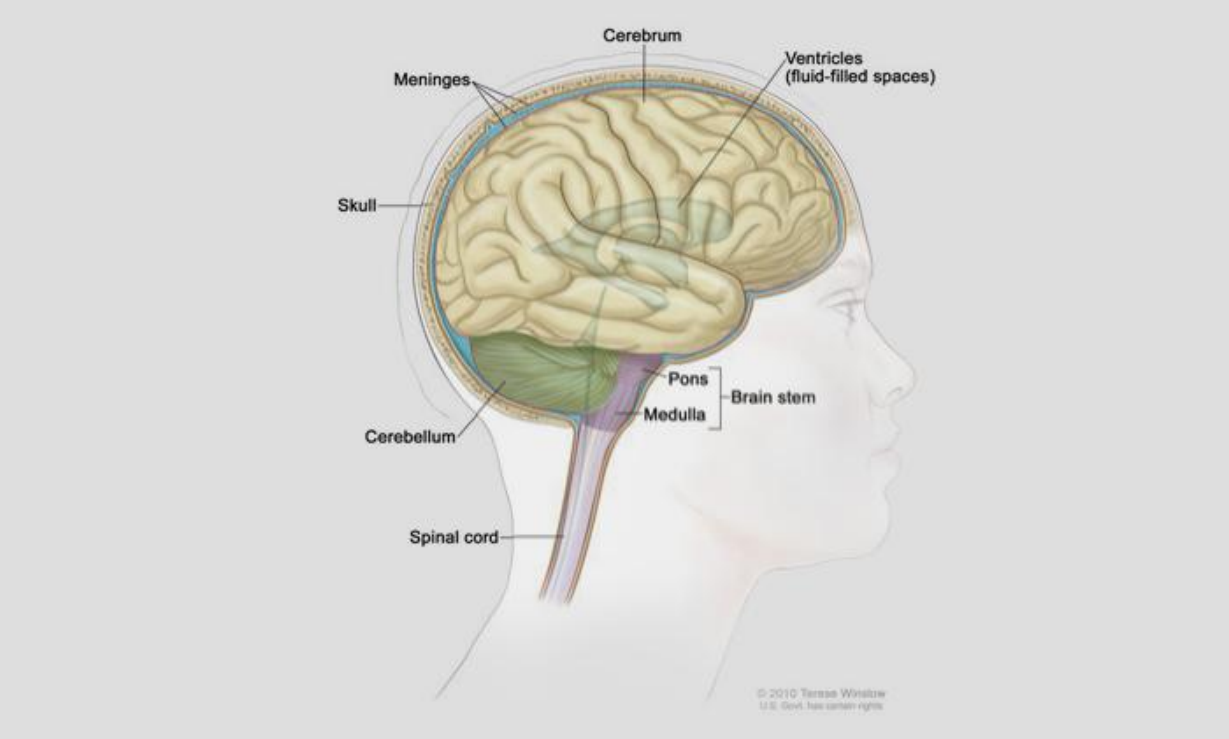

Credit: Ohio State University Medical Center

The altered metabolism of two essential amino acids helps drive the development of the most common and lethal form of brain cancer, according to a new study led by researchers at The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James). The findings

suggest new ways to treat the malignancy, slow its progression and reveal its extent more precisely.

The study shows that in glioblastoma (GBM), the essential amino acids methionine and tryptophan are abnormally metabolized due to the loss of key enzymes in GBM cells.

The altered methionine metabolism leads to activation of oncogenes, while the changes in tryptophan metabolism shield GBM cells from detection by immune cells. Together, the changes promote tumor progress and cancer-cell survival.

"Our findings suggest that restricting dietary intake of methionine and tryptophan might help slow tumor progression and improve treatment outcomes," says first author and OSUCCC - James researcher Kamalakannan Palanichamy, PhD, research assistant professor in Radiation Oncology.

The study is published in the journal *Clinical Cancer Research*.

"While we need to better understand how these abnormally regulated metabolites activate oncogenic proteins, our intriguing discovery suggests novel therapeutic targets for this disease," says principal investigator and study leader Arnab Chakravarti, MD, chair and professor of Radiation Oncology and co-director of the Brain Tumor Program at the OSUCCC - James.

"For example, restoring the lost enzymes in the two metabolic pathways might slow tumor progression and reduce aggressiveness by inactivating oncogenic kinases and activating immune responses," says Chakravarti, who holds the Max Morehouse Chair in Cancer Research.

Chakravarti further notes that because GBM cells take up methionine

much faster than normal glioma cells, positron emission tomography that uses methionine as a tracer (MET-PET) might help map GBM tumors more accurately, allowing more precise surgical removal and radiation-therapy planning. (MET-PET is currently an experimental imaging method.)

More than 11,880 new cases of GBM were estimated to occur in 2015, with overall survival averaging 12 to 15 months, so there is an urgent need for more effective therapies.

Amino acids are the building blocks of proteins. Tryptophan and methionine are essential amino acids - the diet must provide them because cells cannot make them. Normally, the lack of an essential amino acid in the diet can lead to serious diseases and even death. Foods rich in tryptophan and methionine include cheese, lamb, beef, pork, chicken, turkey, fish, eggs, nuts and soybeans.

Palanichamy, Chakravarti and their colleagues conducted this study using 13 primary GBM cell lines derived from patient tumors, four commercially available GBM cell lines and normal human astrocyte cells. Metabolite analyses were done using liquid chromatography coupled with mass spectrometry.

Key technical findings include:

- GBM cells concentrate methionine 5-100 times more than normal human astrocytes;
- Growing GBM cells without methionine slowed their proliferation 40-60 percent;
- Abnormal methionine metabolism leads to aberrant methylation and gene silencing;
- Reinforcing kynurenine catabolic enzymes in the tryptophan pathway might enable immune cells to recognize and destroy

GBM cells.

More information: K. Palanichamy et al. Methionine and Kynurenine Activate Oncogenic Kinases in Glioblastoma, and Methionine Deprivation Compromises Proliferation, *Clinical Cancer Research* (2016). DOI: 10.1158/1078-0432.CCR-15-2308

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