Researchers discover key driver of the spread of cancer to the brain

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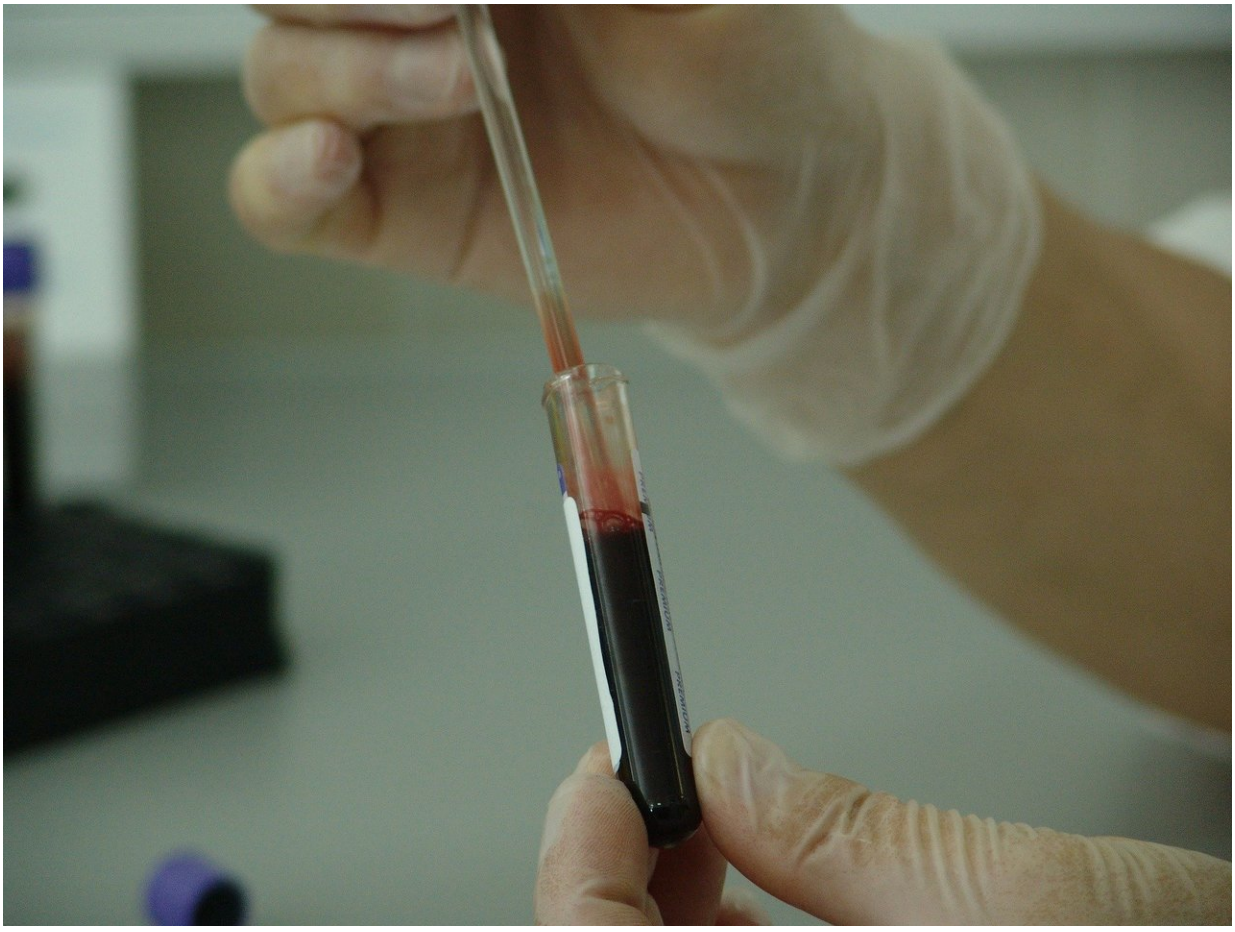

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Approximately 200,000 cancer patients are diagnosed with brain

metastases each year, yet few treatment options exist because the mechanisms that allow cancer to spread to the brain remain unclear. However, a study recently published in the journal *Cancer Cell* by VCU Massey Cancer Center scientist Suyun Huang, M.D., Ph.D., offers hope for the development of future therapies by showing how a poorly understood gene known as YTHDF3 plays a significant role in the process.

Huang is renowned for her work in modeling the spread of cancer to the brain. Her most recent findings show that increased YTHDF3 expression correlates with brain cancer metastases and poor survival outcomes in breast cancer patients. They also demonstrated that the gene is required for multiple steps in the brain metastatic process.

"This study could provide a marker to help doctors diagnose brain metastases early, as well as provide a target for the development of new drugs to prevent and treat brain metastases," says Huang, a member of the Cancer Biology research program at Massey and professor in the Department of Human and Molecular Genetics at VCU School of Medicine.

Huang's team discovered that breast cancer brain metastases have increased YTHDF3 gene copy numbers in comparison to primary breast tumors. A gene's copy number refers to the number of times it appears in the genome. Additional copies of YTHDF3 in metastatic tumor DNA show that mutations have occurred as the cancer cells replicated and spread.

Using a variety of techniques, the researchers profiled the gene to develop a comprehensive view of how it facilitates key processes for brain cancer metastasis through its role in the production of various proteins that interact with the brain microenvironment. Through these experiments, they found that YTHDF3 contributed to the expression of a

number of genes known to drive cancer development, including ST6GALNAC5, GJA1, EGFR and VEGFA. Mouse models lacking the YTHDF3 gene demonstrated prolonged survival and resistance to brain metastasis development.

"Now that we've shown how critical this gene is to the development of brain metastases, we plan to work on synthesizing drugs that can inhibit its function," says Huang. "This is an urgent need, and we're hopeful this research will eventually help save lives."

More information: Guoqiang Chang et al, YTHDF3 Induces the Translation of m6A-Enriched Gene Transcripts to Promote Breast Cancer Brain Metastasis, *Cancer Cell* (2020). DOI: 10.1016/j.ccell.2020.10.004

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