Signaling mechanism could be target for survival, growth of tumor cells in brain cancer

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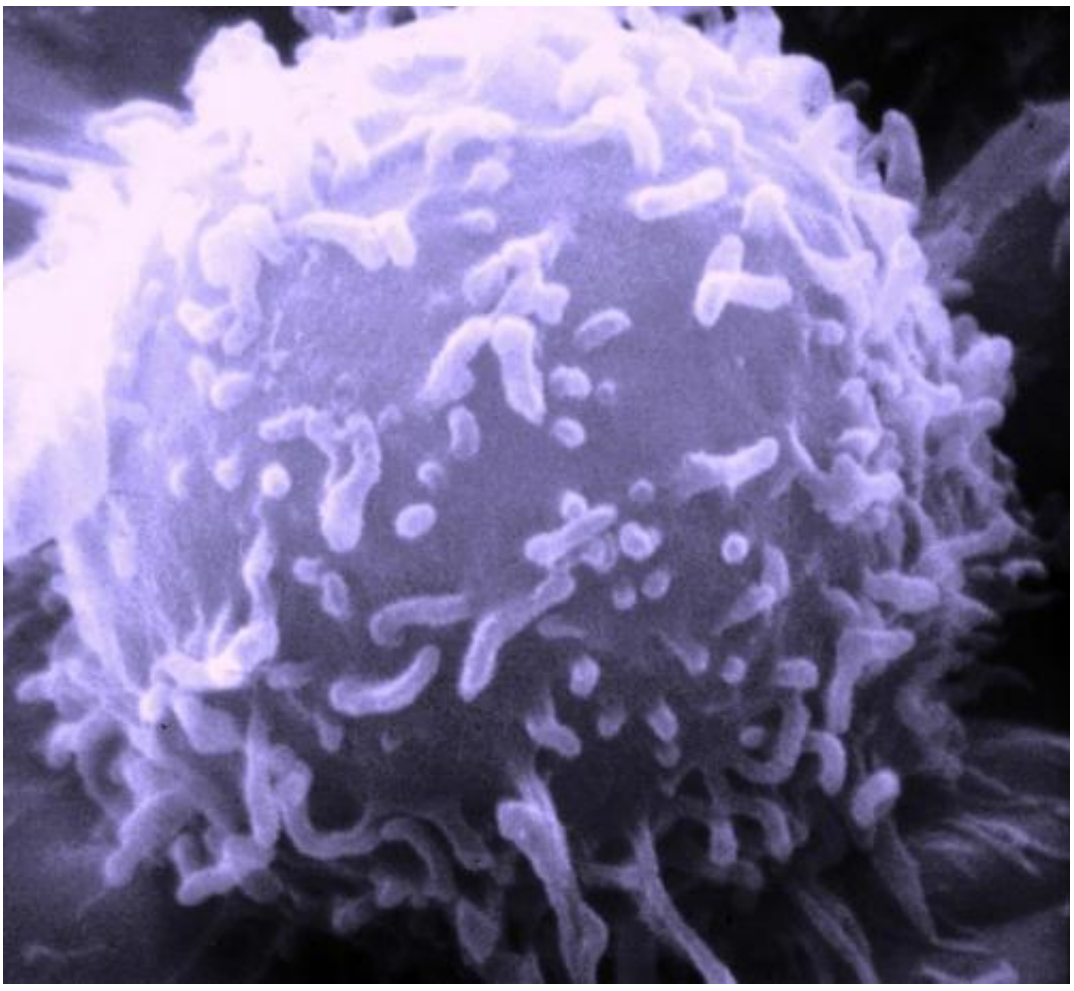

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

UT Southwestern Medical Center neurology researchers have identified an important cell signaling mechanism that plays an important role in brain cancer and may provide a new therapeutic target.

Researchers found that this mechanism—a type of signaling termed constitutive or non-canonical epidermal growth factor receptor (EGFR) signaling—is highly active in glioblastomas, the most common type of adult brain cancer and a devastating disease with a poor prognosis.

When activated in cancer cells, it protects the tumor cells, making them more resistant to chemotherapy treatment. The pathway may also have implications for other types of lung and breast cancers where overexpression of EGFR is a factor.

"Abnormal EGFR signaling, a common and key feature of human cancer, is of considerable interest both for a role in the growth of malignant cells and as a target for treatment," said Dr. Amyn A. Habib, Associate Professor of Neurology and Neurotherapeutics at UT Southwestern and member of the Harold C. Simmons Cancer Center, the only National Cancer Institute-designated cancer center in North Texas and one of just 66 NCI-designated cancer centers in the nation.

Glioblastomas (GBM) arise from astrocytes, which are star-shaped cells that make up the "glue-like" or supportive tissue of the brain, according to the American Brain Tumor Association. They represent about 17 percent of brain tumors, and are more common in males and those over 50.

Fueled by a good blood supply, they grow rapidly, increasing pressure on the brain and causing symptoms such as headaches, vomiting and nausea, speech and memory difficulties, muscle weakness on one side, and vision problems, depending on where the tumor grows in the brain. Due to that fast growth, average survival is just 15 months after diagnosis.

In their study, Dr. Habib and his team shed new light on why this difficult-to-treat cancer can be resistant to treatment.

The epidermal growth factor receptor is frequently amplified and mutated in human cancer, including lung and breast cancer, and plays an important role in the growth of cancer cells and in resistance to chemotherapy.

EGFR becomes activated when the epidermal growth factor (EGF) - its ligand or partner molecule—binds to it and triggers biochemical signals within cells that lead to tumor growth or resistance to treatment. In human cancers, the EGFR may be expressed with or without its ligand or partner.

"We found that brain cancer cells expressing EGFR are more resistant to chemotherapy in the absence of ligand," said Dr. Habib, and a staff physician at the North Texas VA Medical Center.

Specifically, the presence of EGF acts as a switch to turn off non-canonical signaling and turn on ligand-activated signaling. Non-canonical EGFR signaling results in activation of a transcription factor called IRF3. IRF3 activity activates immune signals and normally protects cells from virus infection but when activated in cancer cells may protect tumor cells from chemotherapy. Therefore, the IRF3 signaling network may be a new target for treatment in cancer, Dr. Habib said. For example, blocking IRF3 activation using small molecule inhibitors may be a strategy for stopping growth of tumor cells.

"The non-canonical EGFR signaling network may be an important target for treatment in those cancers in which the level of EGFR ligand is low," he said.

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