STAT3 gene regulates cancer stem cells in brain cancer

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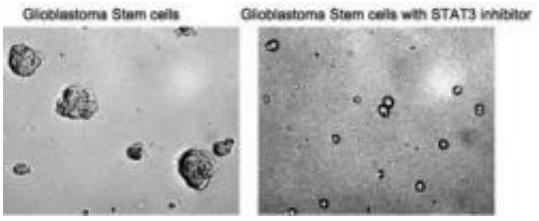

These are glioblastoma stem cells with and without the STAT3 inhibitor. Credit: Tufts University

In a study published online in advance of print in *Stem Cells*, Tufts researchers report that the STAT3 gene regulates cancer stem cells in brain cancer. Cancer stem cells have many characteristics of stem cells and are thought to be the cells that drive tumor formation. The researchers report that STAT3 could become a target for cancer therapy, specifically in Glioblastoma multiforme (GBM), a type of malignant and aggressive brain tumor.

Patients with Glioblastoma multiforme typically survive 12 to 14 months with treatment. Treatment options include radiation, chemotherapy, and surgery.

"When STAT3 is inhibited, cancer stem cells in glioblastomas lose their stem-cell characteristics permanently, suggesting that STAT3 regulates growth and self-renewal of stem cells within glioblastomas. Strikingly, a

single, acute treatment with STAT3 inhibitors was effective, implying that a STAT3 inhibitor could stop tumor formation," said senior author Brent Cochran, PhD, a professor at Tufts University School of Medicine and a member of the cellular & molecular physiology program faculty at the Sackler School of Biomedical Sciences at Tufts.

"STAT3 has been shown to be activated in a number of human tumors. This study is one of the first to show, however, that STAT3 regulates cancer stem cells. It is one of the few genes linked to the propagation of cancer stem cells, and it appears to regulate processes involved in the six hallmarks of cancer: growth, metastasis, angiogenesis, evasion of apoptosis, tissue invasion, and cell immortalization," he continued.

The researchers used cancer stem cells isolated from surgically removed samples of glioblastoma tumors. Cell cultures were treated with two chemically distinct small-molecule inhibitors (STA-21 and S3I-201) of STAT3. After several days of treatment, cell growth in the STAT3-inhibited cultures was minimal compared to growth in the control cultures. Moreover, in the STAT-inhibited cultures, proteins that help maintain stem-cell characteristics were apparently turned off. This finding leads the researchers to believe that STAT3 has a distinct role to play in cancer stem cells, which may make it an especially good target for cancer therapy.

"Current cancer therapies that prolong life do not specifically target cancer stem cells, and these cells are often resistant to traditional radiation and chemotherapies. STAT3 appears to govern the propagation of cancer stem cells in Glioblastoma multiforme. Targeted inhibition of STAT3 in GBM cancer stem cells gives us a new approach to treating this devastating brain cancer," said Julian Wu, MD, associate chairman of neurosurgery and chief of the division of neurosurgical oncology at Tufts Medical Center. He is also a professor at Tufts University School of Medicine. Dr. Wu is known for his expertise in gene therapy for brain

tumors and the molecular genetics of primary and metastatic brain tumors.

"We are encouraged by the potential of STAT3 in our study," said Cochran. "Research has already demonstrated that STAT3 and cancer go hand in hand, but, until this study, we did not know that STAT3 regulates cancer stem cells, which are extremely resistant to conventional therapy. Given these findings, I hope that our future research investigating the mechanisms involved in inhibiting STAT3 will contribute to more effective and less invasive cancer therapies."

More information: Sherry MM, Reeves A, Wu JK, and Cochran BH. 2009. *Stem Cells*. "STAT3 is required for proliferation and maintenance of multipotency in glioblastoma stem cells." Published online August 5, 2009, doi: 10.1002/stem.185

Source: Tufts University