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Blocking PRMT5 might force resistant brain-tumor cells into senescence, study suggests

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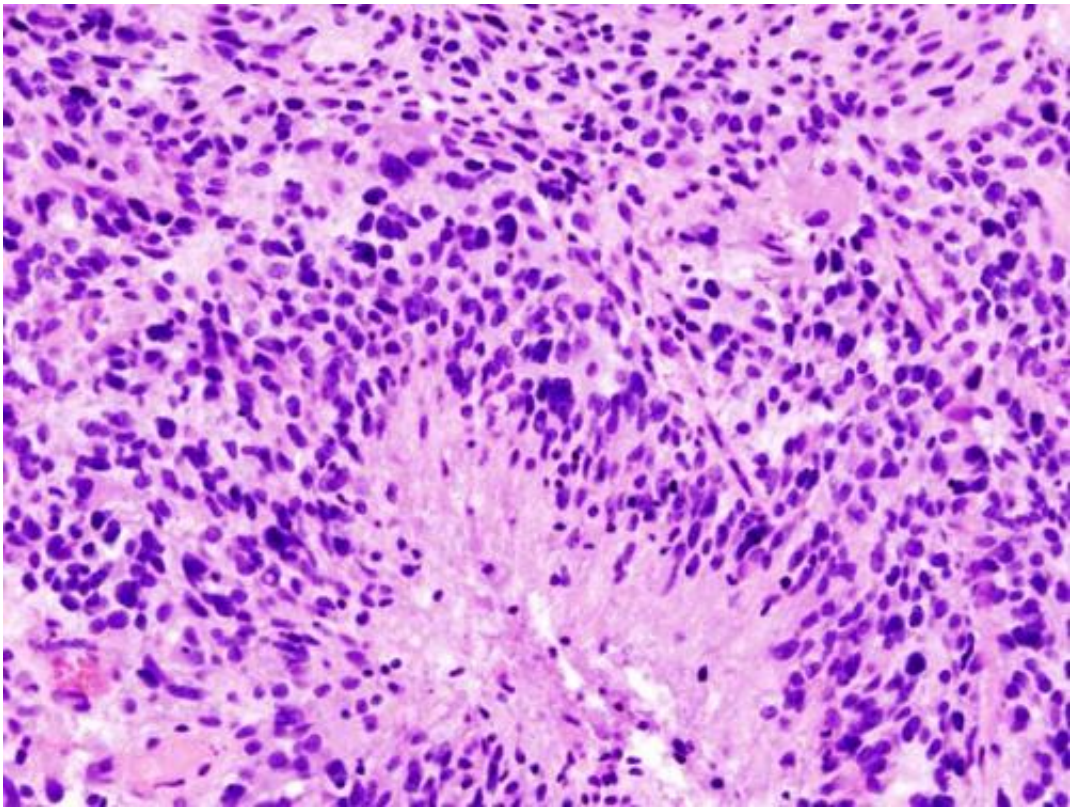

Glioblastoma (histology slide). Credit: Wikipedia/CC BY-SA 3.0

A new study suggests that blocking an enzyme called PRMT5 in tumor cells could be a promising new strategy for the treatment of glioblastoma (GB), the most aggressive and lethal form of brain cancer.

The study by researchers at The Ohio State University Comprehensive

Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James) shows that knocking down PRMT5 (protein arginine methyltransferase 5) might force the cells into senescence and slow or stop tumor growth.

PRMT5 regulates gene transcription and other cell processes by transferring methyl groups and modifying chromatin. Overexpression of the enzyme in GB is associated with more aggressive disease.

The researchers showed that PRMT5 inhibits the activity of a major tumor-suppressor gene called PTEN. Overall, they found that PRMT5 has different roles in undifferentiated cells, where it promotes proliferation, and in differentiated GB cells, where it is essential for cancer-cell survival.

The study is published in the journal *Oncogene*.

"Our findings show that inhibiting PRMT5 can affect both mature and immature tumor cells in glioblastoma, and they underscore the importance of developing PRMT5 inhibitors as a promising therapeutic approach for patients with these tumors," says principal investigator and OSUCCC - James researcher Balveen Kaur, PhD, professor and vice chair of research in the Department of Neurological Surgery at Ohio State.

More than 11,880 new cases of GB were estimated to occur in 2015 in the United States. Despite advances in surgery, radiation and drug therapy, overall survival averages 12 to 15 months. Therapies that are more effective are urgently needed.

One factor thought responsible for poor GB-treatment outcomes is that the tumors consist of immature, undifferentiated, stem-like cells that are resistant to radiation and chemotherapy, along with cells that are more

differentiated and sensitive to therapy.

In this study, Kaur and her colleagues used primary tumor cells from patients and an animal model to examine how loss of PRMT5 affects survival, proliferation, apoptosis (programmed cell death) and senescence in both undifferentiated and differentiated GB cells.

Key findings included:

- In differentiated primary tumor cells, depleting PRMT5 led to cell death by apoptosis;
- In undifferentiated cells, depleting the enzyme led to cell-cycle arrest and senescence;
- In undifferentiated cells, PRMT5 repressed the PTEN tumor-suppressor gene, leading to cell proliferation; PTEN repression was not seen in differentiated cells;
- Inhibiting PRMT5 in tumors transplanted into mice decreased the size and growth rate of the tumors.

Provided by Ohio State University Medical Center