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RESEARCHERS IDENTIFY GENES THAT ALLOW BRAIN CANCER-CAUSING STEM CELLS TO RESIST TREATMENT

LOS ANGELES (Dec. 14, 2006) – While great interest has followed the discovery of neural stem cells and their potential for someday treating diseases and injuries of the brain and spinal cord, recent research identified “cancer stem cells,” a small population of cells that appear to be the source of cells comprising a malignant brain tumor. Theoretically, if these mother cells can be destroyed, the tumor will not be able to sustain itself. On the other hand, if these cells are not removed or destroyed, the tumor will continue to return despite the use of current cancer-killing therapies.

Researchers at Cedars-Sinai Medical Center’s Maxine Dunitz Neurosurgical Institute, who first isolated cancer stem cells in adult brain tumors in 2004, have now found these cells to be highly resistant to chemotherapy and other treatments. Even if a tumor is almost completely obliterated, it will regenerate from the surviving cancer stem cells and be even more resistant to treatment than before.

Results of studies on three established glioma cell lines and tumor tissue removed from five patients at Cedars-Sinai appear in the Dec. 2 issue of the journal *Molecular Cancer*. The researchers describe genes and mechanisms that give cancer stem cells their chemoresistant properties. They also allude to ongoing research aimed at developing methods for readily distinguishing cancer stem cells from normal neural stem cells, which could lead to therapies targeting the cancer-causing cells without damaging healthy ones.

“If one believes in the cancer stem cell hypothesis, this is an extremely important area of investigation. These stem cells are like the mother cells of the tumor, which I think is a very significant observation. It may guide the way we research tumors and the way we look for therapeutic approaches to treat these tumors because all of our efforts will need to be directed at killing these cells,” said Keith L. Black, M.D., neurosurgeon, director of the Maxine Dunitz Neurosurgical Institute and chair of Cedars-Sinai’s Department of Neurosurgery.

Cancer stem cells were first found in certain leukemias and in breast carcinomas. In 2004, shortly after cancer stem cells were identified in pediatric brain tumors, researchers at Cedars-Sinai’s Institute reported the first isolation of cancer stem cells in adult brain tumors.

“Gliomas that are treated with chemotherapy recur with renewed resilience and aggression. Although the drugs kill most of the cells in the tumor, cancer stem cells may be left behind. In this study, we provide the first evidence that cancer stem cells have a significant resistance to conventional chemotherapeutic agents. We also link this resistance to genes that are known to inhibit a cell death process called apoptosis,” said neurosurgeon John S. Yu, M.D., co-director of the Comprehensive Brain Tumor Program at Cedars-Sinai and senior author of the journal article.

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Normal stem cells are “immature” cells that have the potential to become any of several types of cells. Cancer stem cells have the same multi-potent and self-renewing properties, but instead of producing healthy cells, they propagate cancer cells.

Part of the study included a comparison of cells taken from patients’ primary (first-onset) tumors with cells taken from recurring tumor after radiation, chemotherapy and/or immunotherapy. In each of the five cases examined, the recurrent tumors contained much higher concentrations of cancer stem cells, indicating that while many tumor cells may have died, treatment-resistant “source” cells survived and regenerated.

Another finding suggests that cancer stem cells are responsible not only for regeneration of tumor cells but also encourage their migration. Gliomas are extremely difficult to treat because they evade treatment and because they are highly invasive.

“The identification and study of brain cancer stem cells is providing insight into the way tumors form and grow,” said Yu. “This may be a major step toward designing therapies that use brain cancer stem cells as a target, not only to destroy a tumor but to prevent it from coming back.”

The study was funded by grants from the National Institutes of Health.

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Citation: *Molecular Cancer*, Dec. 2, 2006, “Analysis of Gene Expression and Chemoresistance of CD133+ Cancer Stem Cells in Glioblastoma.”

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