Mechanism in cells that generate malignant brain tumors may offer target for gene therapy

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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 identified a molecular mechanism that is involved in the development of these cells from which malignant brain tumors may originate. This could offer a target for scientists seeking treatments that would kill malignant brain tumors at their source and prevent them from recurring.

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. 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 existing cancer-killing therapies.

Glioblastoma multiforme is the most malignant form of tumor that develops in the brain, but not all glioblastomas are identical. Subgroups are comprised of cells originating from different brain tumor stem cells with unique genetic characteristics that use different signaling pathways in their development and growth. The Cedars-Sinai researchers are building genetic "profiles" of these cancer stem cells and the tumors they appear to produce.

In this study, published in the journal *Stem Cells* (*Stem Cells* Express online Sept 11., ahead of print), the researchers identified a subset of brain tumor stem cells that is dependent on a protein called Sonic Hedgehog and another subset that is not Hedgehog dependent. The brain tumors resulting from each subset retained the "signaling dependency" characteristics of the mother cells, and in laboratory experiments and studies in laboratory mice, pathway-specific blocking interventions prevented the brain tumor stem cells from being able to renew themselves.

Although cancer stem cell involvement in the genesis of brain tumors is hypothetical and in the early stages of scientific discovery, the Sonic Hedgehog signaling mechanism appears to be one of the molecular mechanisms regulating both normal stem cell growth and cancer stem cell growth.

"According to our analysis, patients who have malignant brain tumors produced from cancer stem cells that rely on this mechanism have a shorter survival than those who don't," said John S. Yu, M.D., director of Surgical Neuro-oncology at Cedars-Sinai and senior author of the Stem Cells article.

Further investigation of these and other pathways may allow scientists to devise therapies to block the underlying cancer-causing mechanisms with genes or small molecules, according to the research team.

"Understanding the mechanisms behind cancer stem cells, which may be the root and cause of cancers, may allow us to determine how these cancers start and, more importantly, how best to target them to prevent their growth and spread," said Keith L. Black, M.D., chairman of the Department of Neurosurgery, director of the Maxine Dunitz Neurosurgical Institute, and one of the paper's authors.

After isolating cancer stem cells in adult brain tumors in 2004, the Cedars-Sinai researchers in 2006 reported that these cells are 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.

Citation: *Stem Cells*, "Hedgehog signaling regulates brain tumor stem cell self-renewal and portends shorter survival for patients with PTEN-coexpressing glioblastomas," published online Sept. 11, 2008.

Source: Cedars-Sinai Medical Center