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Marrow-derived stem cells deliver new cytokine to kill brain tumor cells, offer protection

LOS ANGELES (EMBARGOED UNTIL 12:01 A.M. EST ON MARCH 1, 2006) – Attaching a recently discovered cytokine to neural stem cells derived from bone marrow, researchers at Cedars-Sinai Medical Center's Maxine Dunitz Neurosurgical Institute have developed a tool to track and kill malignant brain tumor cells and provide long-term protection against their return.

Results of an animal study are published in the March 1, 2006 issue of Cancer Research, and the researchers are now applying to regulatory agencies to translate their work into human clinical trials.

Gliomas are highly invasive tumors with poorly defined borders that intermingle with healthy brain tissue, making complete surgical removal nearly impossible. Furthermore, cells separate from the main tumor and migrate to form satellites that escape treatment and often lead to recurrence.

Researchers at the Maxine Dunitz Neurosurgical Institute documented several years ago that some neural stem cells – "immature" cells that can differentiate into central nervous system cells – have the ability to target and track glioma cells in the brain, even as they migrate. The researchers identified the mechanism that enables certain neural stem cells to develop this tracking ability and genetically engineered neural stem cells to transport several cytokines – proteins that regulate immune responses – to track down and destroy glioma cells.

In 2002, the scientists reported that they had produced central nervous system cells from stem cells derived from bone marrow. Because these stem cells originate in the bone marrow instead of the brain or fetal or embryonic tissue, there is an unlimited supply of cells that are free of ethical and tissue-rejection issues.

This study provides the first documentation that the marrow-derived stem cells possess the same tumor-tracking capability of other neural stem cells. It also includes the first report on the use of the cytokine interleukin-23 (IL-23) as a potential gene-delivered therapy against glioma.

"The paper recapitulates our previous data demonstrating that the neural stem cells – in this case from bone marrow – were able to track to the tumor very efficiently and, like a heat-seeking missile, deliver a killer depot," said John S. Yu, M.D., neurosurgeon, co-director of the Comprehensive Brain Tumor Program at the Maxine Dunitz Neurosurgical Institute, and the article's senior author. "We obtained the stem cells from bone marrow, mirroring what we want to do clinically, which is to take bone marrow cells from a patient, make them into neural stem cells, put in the gene of interest and treat the patient."

In this case, the gene of interest produces IL-23, which appears to be very well suited for attacking gliomas. Earlier studies used IL-4, IL-12, and tumor necrosis factor related apoptosis inducing ligand (TRAIL).

"Each cytokine has unique functions. What we want to do is marry the function with the therapeutic response we want to achieve. Interleukin-23 promotes the function of dendritic cells and memory T-cells, important components in an immune response to tumor cells. The earlier cytokines produced good results, but IL-23 is even more potent," Yu said.

"Most anti-tumor gene strategies attempt to deliver genes directly to tumor cells, but gliomas are especially challenging because of their highly invasive and migratory characteristics," said Keith L. Black, M.D., director of the Maxine Dunitz Neurosurgical Institute, director of Cedars-Sinai's Division of Neurosurgery, and co-director of the Comprehensive Brain Tumor Program. "By combining the tumor-tracking properties of bone marrow-derived neural stem cells with interleukin-23, we are able to initiate a very powerful anti-tumor response that tracks to migrating glioma islands and offers long-term protection – all of which would make this a very attractive therapeutic option."

In the animal study, bone marrow-derived neural stem-like cells (BM-NSC) genetically engineered to produce IL-23 were injected into intracranial gliomas and other areas of the brain. Treated animals survived significantly longer than those in control groups. In

fact, of those receiving BM-NSC-IL-23, 60 percent survived beyond day 120 tumor-free. Only 20 percent of those treated with IL-23 that was not attached to neural stem cells survived, and no animals survived if they received neural stem cells without IL-23.

Even after additional glioma cells were injected, BM-NSC-IL-23-treated animals remained tumor free, evidence of the long-term immunity provided by IL-23's generation of memory T-cells.

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