CEDARS-SINAI MEDICAL CENTER NEWS

Media Contact: Sandra Van
Telephone: 1-800-880-2397
E-mail: sandy@prpacific.com

Citation: *Oncogene*, August, 2005, "Cytotoxic T cell targeting of TRP-2 sensitizes human malignant glioma for chemotherapy."

HIGHLIGHTS:
Researchers at Cedars-Sinai's Maxine Dunitz Neurosurgical Institute recently documented that chemotherapy after immunotherapy provides significantly better results than either therapy can provide alone. Now they offer an explanation for the relative effectiveness of this two-wave assault on malignant brain tumors: chemotherapy sensitivity may be dramatically increased by targeting antigens that are involved in making tumors drug resistant. Results of their study appear in the August issue of *Oncogene.*

CHEMOTHERAPY FOR BRAIN TUMORS IS BOOSTED AFTER VACCINE TARGETS RESISTANCE-RELATED ANTIGEN

LOS ANGELES (June 13, 2005) – In the August issue of the journal *Oncogene*, researchers at Cedars-Sinai Medical Center's Maxine Dunitz Neurosurgical Institute describe a molecular mechanism that appears to make malignant brain tumors more vulnerable to chemotherapy after they have been treated with the dendritic cell vaccine.

This finding builds on several studies recently published by the research team. In 2003, they reported that a protein fragment previously found in melanomas also was detected in highly aggressive brain tumors called glioblastoma multiforme (GBM). The immune system recognizes the peptide, Tyrosinase-Related Protein (TRP)-2, as a foreign invader, making it a significant target for immunotherapy.

"Our findings suggest that TRP-2 could be a powerful molecule linking chemotherapy and immunotherapy," said Keith L. Black, M.D, one of the paper's authors, director of the Maxine Dunitz Neurosurgical Institute and director of the medical center's Division of Neurosurgery and Comprehensive Brain Tumor Program.

"Based on our results, it appears that we can improve chemotherapy sensitivity by targeting TRP-2 and possibly other drug-resistant related tumor antigens. This may be a significant step in the fight against brain tumors and other malignant cancers because even as we have been able to develop very powerful and targeted chemicals, tumors have often been able to outmaneuver them," said Black.

In 2004, the researchers documented that the combination of immunotherapy and chemotherapy significantly slowed tumor progression and extended survival of patients suffering from these deadly tumors. The two therapies together were able to accomplish results that neither could achieve by itself. The average length of survival was extended to about 26 months, compared to 18 months for patients who received vaccine alone and 16 months for those undergoing chemotherapy alone.

In a number of laboratory and clinical trials, dendritic cell immunotherapy had succeeded in eliciting a powerful immune response against brain tumor cells, but significant improvements in length of survival had

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not been realized. One theory is that the rate at which tumor cells die is too slow to keep pace with the rapid growth and mutation of tumors in the body. Similarly, chemotherapy directed against GBM has had very little effect. Even new agents specifically designed to attack the DNA of tumor cells and prevent their replication fail or became impotent as the tumor cells developed drug resistance.

Taking into account recent articles identifying TRP-2 as a contributing factor in the ability of tumor cells to mutate and resist a variety of therapeutic drugs, the Cedars-Sinai team now offers an explanation for the relative effectiveness of this two-wave, vaccine-chemotherapy assault. The first attack comes from the dendritic cell vaccine that is specially formulated to search and destroy tumor cells that contain TRP-2. It clearly launches "cytotoxic T lymphocytes," tumor cell-killing immune cells that diminish or deplete the number of TRP-2-containing tumor cells. Other GBM cells survive, however, and continue to proliferate. But because they lack TRP-2 and therefore the ability to develop drug resistance, they are vulnerable in the follow-up assault of chemicals targeting their DNA.

John S. Yu, M.D., senior author of the paper and co-director of the Comprehensive Brain Tumor Program, said lab results confirmed a strong immune response to TRP-2 in patients' blood cells after vaccination, and cells removed from tumors after vaccination had significantly lower TRP-2 expression than did those removed earlier. Furthermore, the post-vaccine tumor cells were much more sensitive to anti-tumor drugs.

"It is important to note also that four patients in our study that demonstrated a response to TRP-2, after tumor recurrence, responded to chemotherapy with what oncologists call complete responses, which means the tumors were no longer visible on MRI," he added. "This was a small initial study and it will be very interesting to see if similar results will be repeated in larger numbers."

Dendritic cell vaccination, pioneered at Cedars-Sinai in the treatment of GBM, introduces foreign proteins from surgically removed tumors to dendritic cells, which are also called antigen-presenting cells because they identify foreign material for destruction by cell-killing T lymphocytes. The tumor cells are cultured with the dendritic cells in the laboratory to enable the immune cells to recognize cancer cells as targets. When the resulting "specialized" dendritic cells are injected back into the patient, they seek out remaining tumor cells and signal for the T lymphocytes to destroy them.

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