CEDARS-SINAI MEDICAL CENTER NEWS

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HIGHLIGHTS:
Scientists seeking better ways to enlist the immune system in the battle against malignant brain tumors have a new target – an antigen that was previously detected in melanomas. A recent study found that the TRP-2 antigen was expressed at significant levels in glioma cells and that a strong immune response could be triggered against it.

ANTIGEN TARGETED IN THERAPY FOR MELANOMA ALSO PROMPTS IMMUNE RESPONSE IN BRAIN TUMOR CELLS

LOS ANGELES (Sept. 24, 2003) – A protein fragment that was previously found in melanomas has now been detected in highly aggressive brain tumors called gliomas that take the lives of about 15,000 Americans each year.

This peptide, which the immune system recognizes as an antigen, or foreign invader, appears to be a target for anti-tumor immune therapy, according to studies conducted by researchers at Cedars-Sinai's Maxine Dunitz Neurosurgical Institute and the National Cancer Institute. It also may be useful as a marker that will enable scientists to monitor immune responses in human clinical trials against cancer cells called glioblastoma multiforme (GBM), often referred to as gliomas.

Institute scientists and neurosurgeons have for several years conducted clinical trials using immunotherapy techniques to battle gliomas, removing brain tumor cells and culturing them with immune system cells called dendritic cells in the lab. When the resulting "vaccine" is injected into the patient's bloodstream, the dendritic cells recognize the tumor cells as invaders and "present" them to the antigen-fighting T-lymphocytes, triggering an immune response.

"The outlook for patients who suffer from these highly aggressive tumors has historically been extremely poor, and even conventional treatments such as surgery, chemotherapy and radiation therapy have provided almost no benefit," said Keith L. Black, M.D., neurosurgeon and founder and director of the Institute. "Based on the

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results of our early studies, the immune system appears to have the potential to destroy glioma cells and contribute to longer periods of patient survival. Unfortunately, the immune system is not very effective on its own. Therefore, we are always looking for new ways to target and boost the immune response."

In mouse and human studies of melanoma, tyrosinase-related protein-2 (TRP-2) has proved to be an excellent target for immunotherapies. This study found that the TRP-2 antigen also was expressed at significant levels in glioma cells and that a strong immune response could be triggered against it.

Tests were conducted on the genetic material of established glioma cell lines and on cells of brain tumors removed from patients undergoing treatment at the Maxine Dunitz Neurosurgical Institute. Lab results demonstrated that TRP-2 protein was expressed in primary cultured glioma cells and in fresh tissue.

Additional tests found that certain cytotoxic T lymphocytes – immune system cells that attack invaders – were able to recognize TRP-2 as a target when TRP-2 was expressed in significant levels. The degree of recognition correlated with the level of TRP-2 expression in the genetic material, an important finding because TRP-2 is expressed to lesser degrees – below the recognition and immune activation threshold – in normal brain tissue.

The researchers also were able to generate in the laboratory an immune response using blood cells and dendritic cells from a healthy donor and specially prepared TRP-2-positive glioma cells. The immune cells were able to recognize the TRP-2 positive GBM tumor cell lines, and an increase in TRP-2-specific antigen-killing activity could be seen. The identification of TRP-2 as a brain tumor-associated antigen appears, therefore, to offer not only a new target for immunotherapy, but a way to monitor related immune responses.

An increase in TRP-2-related immune activity also was detected in four patients with malignant brain tumors who were part of a clinical trial at the Maxine Dunitz Neurosurgical Institute. Cytotoxic T lymphocyte activity was significantly increased after three dendritic cell vaccinations, and the patients appeared to have no adverse effects from the vaccinations.

Research scientist Gentao Liu, Ph.D., was the paper's first author. Other Institute contributors included research scientist Christopher J. Wheeler, Ph.D.; John S. Yu, M.D., co-director of the Comprehensive Brain Tumor Program; Dr. Black, who directs the medical center's Division of Neurosurgery and the Comprehensive Brain Tumor Program and holds the Ruth and Lawrence Harvey Chair in Neuroscience; and research scientist Han Ying, Ph.D. Hung T. Khong, M.D., a contributing author from the Surgery Branch of the National Cancer Institute, was involved in previous discoveries of TRP-2 in melanoma.

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Cedars-Sinai is one of the largest nonprofit academic medical centers in the Western United States. For the fifth straight two-year period, it has been named Southern California's gold standard in health care in an independent survey. Cedars-Sinai is internationally renowned for its diagnostic and treatment capabilities and its broad spectrum of programs and services, as well as breakthroughs in biomedical research and superlative medical education. Named one of the 100 "Most Wired" hospitals, the Medical Center ranks among the top 10 non-university hospitals in the nation for its research activities.

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