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HIGHLIGHTS:

“Age-dependent outcome” has described the fact that age at diagnosis was the best predictor of tumor recurrence and survival for cancer patients. Now researchers have documented that recently-produced cancer-fighting cells are the major determinant of prognosis and survival for patients with malignant brain tumors called glioblastoma multiforme (GBM). The thymus provides the majority of cells destined to become antigen-specific cancer-fighting lymphocytes, which are normally a small fraction of CD8+ T lymphocytes. Patients with high numbers of recently generated CD8+ T lymphocytes respond more favorably to immune therapy vaccine.

AGE-RELATED OUTCOMES, IMMUNE RESPONSE IN PATIENTS WITH BRAIN TUMORS LINKED TO THYMIC CELLS

LOS ANGELES (Nov. 17, 2003) – Chronological age at time of diagnosis has long been associated with a patient’s prognosis and length of survival in the battle against brain tumors and other cancers. Older patients typically respond less favorably to treatment and have comparatively poorer outcomes than their younger counterparts.

Physicians and researchers who treat and study cancers, such as a type of incurable malignant brain tumor called glioblastoma multiforme (GBM), describe this as “age-dependent outcome.” Now researchers at Cedars-Sinai’s Maxine Dunitz Neurosurgical Institute have directly linked this age factor to immune system cells recently produced by the thymus gland. Quantifying the number of these new thymus-derived lymphocytes actually provides a more accurate prediction of outcome than does patient age, and finding ways to boost these numbers may become a strategy for improving the ability of immunotherapy to fight cancer.

A more apt description than “age-dependent outcome” is “CD8+ recent-thymic emigrant-dependent outcome,” according to an article in the Nov. 1 issue of the *Journal of Immunology*. CD8+ T lymphocytes, which attack foreign invaders, develop in the thymus and elsewhere. They also replicate in the blood stream to maintain an adequate supply as their production diminishes with advancing age. Those that have recently entered the bloodstream from the thymus are called recent thymic emigrant (RTE) CD8+ T lymphocytes.

“Our findings suggest that levels and function of newly produced recent thymic emigrant CD8+ T cells

(more)

critically influence age-dependent mortality and exert one of the strongest known influences on outcome,” said Keith L. Black, M.D., director of the Maxine Dunitz Neurosurgical Institute and Cedars-Sinai’s Division of Neurosurgery and the Comprehensive Brain Tumor Program.

“Although these cells typically make up only a small fraction of the total number of CD8+ lymphocytes in the blood, they appear to be the ones that provide the most clinically beneficial anti-tumor immune responses,” added Dr. Black, who holds the Ruth and Lawrence Harvey Chair in Neuroscience at Cedars-Sinai.

By quantifying the number of cells harboring CD8+ “T cell receptor excision circles” or TRECs, scientists can establish the number of CD8+ T lymphocytes that have recently emerged from the thymus.

The researchers used TREC analysis to quantify CD4+ and CD8+ recent-thymic emigrant T cells in 44 patients with GBM, the most aggressive of malignant brain tumors called gliomas. Twenty-four of these patients were newly diagnosed, while 18 had recurring disease. Seventeen of the patients were enrolled in immunotherapy vaccine trials.

Although thymic output of T cells declines as part of the normal aging process, and this decline parallels an increase in cancer progression, the specific impact of immunity on human tumor progression in general is not well understood. Because 11 of the vaccine trial patients were evaluated for immune activity against protein fragments common to a variety of human tumors, the researchers were able to examine the role of thymus output in age-dependent GBM outcome and anti-tumor immunity in general.

Patient statistics were analyzed by age and levels of RTE CD8+ T lymphocytes to determine the ability of each of these factors to predict GBM outcome independent of the other. High CD8+ levels predicted longer recurrence-free periods and overall survival in patients who were grouped by similar ages. In contrast, lower patient age failed to predict outcomes in groups of patients who had similar RTE CD8+ levels. Based on this analysis, age predicts tumor outcome so well only because it loosely corresponds to CD8+ TREC levels. This implies that RTE CD8+ T cells are entirely responsible for older glioblastoma patients suffering such poor prognoses.

High levels of CD8+ TRECs also correlated with improved patient response to immune therapy. Researchers at the Maxine Dunitz Neurosurgical Institute have for several years provided experimental treatment using dendritic cell immunotherapy to enhance the immune system’s ability to recognize and attack malignant brain cancer cells. In these studies, patients who had high CD8+ TREC levels were significantly more likely to respond to tumor antigens when they were vaccinated, and additional analysis showed that TREC-bearing CD8+ T cells directly influenced anti-tumor responses. This provides a long-sought link between immune responsiveness and clinical disease course in vaccinated cancer patients.

According to analysis of vaccinated GBM patients, the most accurate correlate of clinical outcomes was the number of CD8+ RTEs proliferating over a relatively short time span. “This proliferation is tightly associated with anti-tumor responses after vaccination,” said Christopher J. Wheeler, Ph.D., research scientist and senior author of the paper. “The evidence suggests that the most clinically effective anti-tumor responses are those mediated directly by newly-produced CD8+ T cells.”

Several of the observations from the human data were confirmed in a study using mice that have normal CD8+ T cell activity in the bloodstream but reduced output of CD8+ T cells by the thymus. Glioma cells were implanted into the brains of middle-aged and aged mice as well as controls. The reduced production of new CD8+ T cells by the thymus led to more rapid tumor growth, but only in aged mice with naturally shrunken

thymuses. These results establish that diminished CD8+ T cell production causes increased mortality in older tumor hosts.

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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. The Medical Center ranks among the top 10 non-university hospitals in the nation for its research activities.

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