



**Citation:** *Cancer*, August 2004, “Association between Laminin-8 and Glial Tumor Grade, Recurrence, and Patient Survival.”

**HIGHLIGHTS:**

A molecular change that occurs as brain tumors progress may give clinicians a way to more precisely evaluate tumor grade and more effectively predict time to recurrence and length of patient survival. Because the protein involved appears to encourage the growth of blood vessels that support tumor development, it is considered a potential target for therapeutic intervention. Results of the study appear in the August issue of *Cancer*.

**JOURNAL *CANCER*: PROTEIN SHIFT PREDICTS BRAIN CANCER GRADE, RECURRENCE AND PATIENT SURVIVAL**

**LOS ANGELES (June 18, 2004)** – Study results published in the August issue of the journal *Cancer* reinforce previous findings that the laminin-8 genes and the resulting protein may be highly valuable targets in the fight against malignant brain tumors.

Researchers at Cedars-Sinai’s Maxine Dunitz Neurosurgical Institute report that over-expression of laminin-8 can be used as a predictor of a tumor’s grade, its potential for recurrence, and the patient’s length of survival. This follows their earlier findings that laminin-8 is up-regulated in the most aggressive brain tumors, glioblastoma multiforme (GBM), and that the gene promotes the tumor cells’ ability to invade neighboring tissue.

The thin “basement membrane” that lies beneath the surface layer of blood vessels contains proteins called laminins. Fifteen laminins have been identified to date. The Cedars-Sinai researchers found that during tumor progression, laminin-9, which is expressed weakly in normal brain tissue and low-grade glial tumors, switched to laminin-8, and the level of expression of the laminin-8 increased significantly, depending on brain tumor grade.

Gliomas develop from glial cells, which make up the supportive tissue of the brain. Different forms of gliomas are further classified by their specific cells of origin and characteristics. The average survival time for patients with Grade 1 or Grade 2 gliomas is six to eight years. For anaplastic astrocytomas (Grade 3 gliomas), survival time decreases to three years, and for Grade 4 astrocytomas, called glioblastoma multiforme (GBM), survival length typically ranges from 12 to 18 months. GBM cells proliferate uncontrollably, aggressively infiltrating nearby tissue. As a GBM progresses, portions of the tumor often outgrow the blood supply but new blood vessels form. The development of these new vessels, a process called angiogenesis, enables the tumor to grow unchecked.

(more)

In this study, Cedars-Sinai researchers, in conjunction with colleagues in Japan, Sweden and Germany, analyzed a variety of gliomas of both high and low grades, as well as normal brain tissue samples. Low-grade astrocytomas and normal brain tissue were found to express very low levels of laminin-9 and virtually no laminin-8. The levels of expression of both variants increased in Grade 3 gliomas, and as gliomas progressed to Grade 4, laminin-8 expression increased significantly and laminin-9 levels tended to decline.

The particular isoform (laminin-8 or laminin-9) predominantly expressed in Grade 4 gliomas appeared to correlate with time to recurrence after tumor-removal surgery. Among patients with high laminin-8 expression, tumors recurred about 4 months after surgery, compared with more than 11 months among patients whose tumors expressed laminin-9 predominantly. Patients with higher levels of laminin-8 also had shorter lengths of survival, averaging about 11 months, compared to 16.7 months when laminin-9 was predominant.

“Historically, the diagnosis of glioblastoma multiforme has come with an extremely poor prognosis, and traditional treatments have had very limited impact on patient survival,” said Keith L. Black, MD, director of the Maxine Dunitz Neurosurgical Institute, Cedars-Sinai’s Division of Neurosurgery and the Comprehensive Brain Tumor Program.

“Only in recent years have we begun to see progress, which is coming from a better understanding of genetic, molecular and immunologic changes that enable these deadly tumors to grow,” said Dr. Black, who holds the Ruth and Lawrence Harvey Chair in Neuroscience at the medical center. “Although a number of genes and proteins have been identified as having altered expression in glial tumors, few have become reliable indicators that can be used to improve diagnosis, prognosis and treatment.”

Julia Y. Ljubimova, MD, PhD, research scientist at the Institute and first author of the *Cancer* article, said the over-expression of laminin-8 may prove to be one of those important markers. Taken in consideration with other genes known to support tumor growth, it may give clinicians measurable clues for predicting recurrence and survival times of patients with high-grade gliomas.

“The switch from laminin-9 to laminin-8 expression, with its gradual increase from a low level of expression in low-grade tumors to a moderate level of expression in Grade 3 gliomas to a significantly high level of expression in 74 percent of GBMs, may be associated with the development of new tumor-feeding blood vessels, contributing to tumor aggressiveness,” she said. “Therefore, laminin-8 appears to be a promising marker of tumor progression. Perhaps more importantly, we hypothesize that if laminin-8 plays a major role in tumor progression and recurrence, it could be an important target for the development of new therapies.”

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

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