CEDARS-SINAI MEDICAL CENTER NEWS

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HIGHLIGHTS:
A molecular change that takes place in the newly formed blood vessels of progressing brain tumors has now been documented in the most common type of breast cancer, as well. The molecular shift occurs in major proteins called laminins, important constituents of blood vessels. As tumors become increasingly invasive, the laminins normally found in blood vessels become altered in the blood vessels of the tumors as part of a process that enables the tumors to grow and metastasize. Observing these changes in the tissue of individual patients may offer physicians a way to accurately diagnose breast carcinoma and predict further development. The molecular mechanism itself is seen as a future target for therapy aimed at cutting off the oxygen and nutrients tumors require.

MOLECULAR CHANGE OCCURRING DURING BRAIN TUMOR PROGRESSION ALSO EVIDENT IN BREAST CANCER

LOS ANGELES (May 2, 2005) – A molecular change that takes place during the progression of malignant brain tumors also occurs in breast cancer, according to a study conducted at Cedars-Sinai's Maxine Dunitz Neurosurgical Institute. The shift appears to be part of a process that enables tumors to develop the new blood vessels they need to grow rapidly, migrate and invade other tissue.

Although the switch is evident even in an early stage of breast cancer when cells are proliferating but not infiltrating normal tissue, it becomes more pronounced as the cancer progresses to the invasive stage. Therefore, the genes involved and the proteins they produce may become markers that physicians can use to determine disease progression and patient prognosis. They also may become targets for new therapies.

The switch affects proteins called laminins, which are components of the "basement membrane" of blood vessels, a thin mesh-like structure beneath the cells of the blood vessel surface (epithelium). Although the surface cells and the basement membrane are distinct entities, they affect each other through biochemical interactions. In fact, the cells actually influence the composition of the basement membrane, and the membrane, in addition to serving as a scaffold for cell attachment, regulates cell behavior, proliferation and migration.

The laminin molecule is composed of three chains – designated alpha (α), beta (β) and gamma (γ) – that are linked together in various combinations to form 15 known isoforms or types of laminin. Each isoform has distinct characteristics and functions. Isoforms are known to change in normal tissues at various stages of development but they also have been found to shift in the presence of several invasive cancers. This shift coincides with blood vessel changes that encourage tumor growth and metastasis.

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Over the past several years, Cedars-Sinai researchers published several articles related to their findings that the beta chain of laminins changed as brain tumors called glioblastoma multiforme progressed. Specifically, laminin-9 (α4β2γ1) switched to laminin-8 (α4β1γ1). Not only did the change occur, but as a brain tumor's grade advanced, the expression of laminin-8 increased significantly.

Now, in their study of breast cancer, the researchers documented for the first time that laminin-9 switched to laminin-8, and laminin-11 (α5β2γ1) switched to laminin-10 (α5β1γ1) as non-invasive ductal carcinoma *in situ* progressed to the invasive ductal carcinoma (IDC), the type of breast cancer that accounts for about 80 percent of cases. The shift in these laminins and the presence of another isoform (laminin-2) also were seen in breast cancer cells that had metastasized to the brain.

"Although the exact mechanism causing these shifts has not yet been defined, the overexpression of laminin-2, laminin-8 and laminin-10 strongly relates to the development of breast cancer-induced neovascularization and tumor progression," said Keith L. Black, M.D., director of the Maxine Dunitz Neurosurgical Institute and one of the paper's authors. "Determining the relative expression of β1 to β2 chains may be useful in diagnosing the stage and progression of breast cancer, predicting additional tumor growth and metastasis, and determining patient prognosis."

An aggressive tumor would quickly outgrow its source of nutrients and oxygen if not for the interaction between the blood vessel cells and the basement membrane to ensure a constantly renewing supply of small vessels, said Black, who directs the medical center's Division of Neurosurgery and the Comprehensive Brain Tumor Program. But in one of their laboratory studies of brain tumor tissue, the researchers were able to reduce tumor cells' ability to invade neighboring tissue by blocking the expression of the laminin-8 gene.

"Like malignant brain tumors, primary and metastatic breast tumors depend on angiogenesis, the tumor-driven creation of new blood vessels. Now we have found that similar molecular changes happen in highly vascular and invasive tumors such as breast and brain cancers," said Julia Y. Ljubimova, M.D., Ph.D., research scientist and senior author of the article. "Anti-angiogenic therapy that seeks to impede the development of the tumor's vascular network is one of the relatively new and promising approaches in the treatment of solid tumors. The molecular mechanisms that contribute to tumor proliferation may prove to be targets for therapeutic intervention."

"The importance of the present paper is that this is the first demonstration of specific laminin isoform changes in pre-cancerous (ductal carcinoma *in situ*) and invasive ductal carcinoma as well as its metastases, in comparison with normal breast tissues," said Shikha Bose, M.D., an expert breast pathologist who participated in the study. "β1 chain of laminin-2, -8 and -10 is detected in newly formed tumor vessels and might be important predictors for patient outcome."

One of only four hospitals in California whose nurses have been honored with the prestigious Magnet designation, Cedars-Sinai Medical Center is one of the largest nonprofit academic medical centers in the Western United States. For 17 consecutive years, it has been named Los Angeles' most preferred hospital for all health needs in an independent survey of area residents. 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 and was recently fully accredited by the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). Additional information is available at www.cedars-sinai.edu.

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