M. D. Anderson team identifies new oncogene for brain cancer

July 2 2007

An overexpressed gene found at the scene of a variety of tumors is implicated in the development of two types of malignant brain cancer in a paper by researchers at The University of Texas M. D. Anderson Cancer Center to be published in the Proceedings of the National Academy of Sciences. The paper will be posted online at the PNAS web site the week of July 2.

“Just because a gene is associated with cancer doesn’t mean that it’s actually causing cancer. In this paper we show for the first time that insulin-like growth factor binding protein 2 (IGFBP2) connects with two other proteins to fuel development and progression of brain tumors,” says senior author Wei Zhang, Ph.D., professor in M. D. Anderson’s Department of Pathology.

Using a gene transfer delivery system in a mouse model, a team led by Zhang and Professor of Pathology Gregory Fuller, M.D., Ph.D., shows that IGFBP2 plays an active role in the tumorigenesis of astrocytoma and oligodendroglioma. Both cancers are forms of glioma, cancers that develop in the glial cells – which normally support and nourish neurons -- that are highly resistant to treatment.

“This makes IGFBP2 an important candidate for development of targeted therapy to treat gliomas,” Zhang says. Gliomas kill about 13,000 people in the United States annually.

The possibilities are not limited to brain cancer, Fuller notes, “because of

the pervasive overexpression of IGFBP2 documented in other cancer types." The gene is expressed only at low levels in normal cells, which would potentially reduce side effects caused by a treatment that targeted the gene or its protein product.

Fuller and Zhang first associated overexpression of the gene with brain cancer in 1999. Other researchers have since found it to be overexpressed in prostate, ovarian, breast and colorectal cancers, some leukemias, and also in drug-resistant tumors.

Overabundance of IGFBP2 has since been shown to be an indicator of poor prognosis for glioma patients. The PNAS paper takes it beyond this biomarker status.

Zhang, Fuller and colleagues employed a viral gene transfer delivery agent known as RCAS, which is loaded with the gene, or genes, of interest and injected into the mouse brain. The viral particles infect only glial cells, where the genes are expressed.

This system allows the researchers to observe whether a gene identified in a correlation study plays an active role in tumorigenesis. It also permits the delivery and study of combinations of genes.

They found that a combination of IGFBP2 and another known oncogene called K-Ras leads to development of astrocytomas – a glioma named for the star-like shape of its constituent cells.

A combination of K-Ras and a third gene, Akt, previously had been shown to develop astrocytomas. Activation of Akt fuels cell growth and survival. None of the three genes caused brain cancer formation when delivered alone. The researchers tried a combination of Akt and IGFBP2 and no tumor formed, suggesting that the two genes lie in the same molecular pathway and have a similar effect.

For oligodendroglioma, the researchers found that IGFBP2 combined with platelet-derived growth factor beta (PDGFB) results in a higher-grade form of the cancer than that caused by PDGFB alone. The high-grade tumors formed by the combination were indistinguishable in their shape and brain-invasive behavior from human oligodendrogliomas.

The combination also activated the Akt pathway, which PDGFB does not induce by itself. Combined with their earlier findings, this led the team to hypothesize that IGFBP2 activates the Akt pathway, which they confirmed in subsequent lab experiments.

In a final experiment, they treated IGFBP2-PDGFB infected cells in culture with a known Akt inhibitor, which killed more of the combination cells than those infected only with platelet-derived growth factor.

This connection to Akt, the researchers note, makes the presence of IGFBP2 in blood serum a potential biomarker that would indicate an active role for Akt in a patient's cancer and thus a role for Akt inhibitors in their treatment.

"The survival of the most advanced stage of glioma, gliobastoma, has not significantly improved for decades," note Zhang and Fuller. "We hope IGFBP2 will provide an effective target for treatment of this devastating disease."

Source: University of Texas M. D. Anderson Cancer Center