UT SOUTHWESTERN MEDICAL CENTER NEWS

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EMBARGOED UNTIL 11:05 P.M. CDT, TUESDAY, MARCH 31, 2009

UT Southwestern researchers find marker for severity in adult brain cancer

DALLAS – April 1, 2009 – Researchers at UT Southwestern Medical Center have identified a new biological indicator that may help identify which brain-cancer patients have the most aggressive forms of the disease.

The researchers found that an inflammation-related molecule called RIP1 is commonly found in high levels in glioblastoma, the most common primary malignant brain tumor in adults. The protein RIP1 is a component of the complex NF-kB signaling network – a family of proteins that play a key role in inflammation-induced cancer.

The study, available online and published in the April issue of *Cancer Research*, could provide a new target for therapeutic drugs for glioblastoma patients who have a high level of RIP1 in their tumors coupled with NF-kB activation.

"This is the first report of high RIP1 levels being associated with any type of cancer," said Dr. Amyn Habib, assistant professor of neurology at UT Southwestern and the study's senior author. "Our data suggests that increased expression of RIP1 could serve as a marker to identify patients who have a significantly worse prognosis and who will likely be resistant to chemotherapy."

Glioblastoma multiforme (GBM), a cancer of the supportive tissue of the brain, is resistant to treatment. GBM can infiltrate the brain extensively and sometimes become large before turning symptomatic. The median survival of patients with GBM is about 15 months after diagnosis, even with radiation and chemotherapy treatments.

In the study, researchers examined tumor tissues from 92 patients to determine the distribution of RIP1 in each. They found that the most malignant form of the tumors, which also are the most common, had highest levels of RIP1.

One of the next steps is to determine whether these patients may respond better to drugs targeting the NF-kB network. There are many drugs currently available that target these proteins.

Another significant finding of the study is the protein RIP1 regulates the function of p53, a tumor suppressor gene that inhibits the growth of tumors.

"RIP1 activates NF-kB and then that increases the expression of a gene called *mdm2*, which

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inhibits the p53 gene," Dr. Habib said. "Inhibition of p53 allows cells with damaged DNA to proliferate and potentially to become cancerous."

Dr. Habib cautioned that the results are preliminary and more research is needed to investigate possible therapeutic strategies.

"We've found a correlation," Dr. Habib said. "If RIP1 is increased, patients do worse; however, we don't know whether this molecule has some causal role in pathogenesis."

Other UT Southwestern researchers involved in the study were co-lead author Dr. Seongmi Park, postdoctoral fellow in radiation oncology; co-lead author Dr. Kimmo Hatanpaa, assistant professor of pathology; Dr. Yang Xie, assistant professor of clinical sciences; Dr. Bruce Mickey, professor of neurological surgery and of otolaryngology – head and neck surgery; Dr. Christopher Madden, assistant professor of neurological surgery; Dr. Jack Raisanen, associate professor of pathology; Dr. Guanghua Xiao, assistant professor of clinical sciences; Dr. Debabrata Saha, assistant professor of radiation oncology; Dr. David Boothman, professor of pharmacology and radiation oncology; Dr. Dawen Zhao, assistant professor of radiology; and Dr. Robert Bachoo, assistant professor of neurology. Drs. Boothman, Habib, Xie and Bachoo are also affiliated with the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern.

The research was partly funded by a grant from the Department of Energy.

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