Trends in Medical Research

ISSN 1819-3587

Academic Journals Inc.

www.academicjournals.com

Most Common Adult Brain Cancer Linked to Gene Deletion, Doctors Say

A study fast-tracked for online publication Dec. 22 in the New England Journal of Medicine has identified an important gene deletion in up to one of every four cases of glioblastoma, the most common adult brain cancer. This deletion contributes to tumor development, promotes resistance to therapy and considerably worsens a patient's survival prospects.

The deletion of the gene, known as NFKBIA, triggers biochemical processes similar to those resulting from a better-known aberration common in glioblastomas: alteration of the epidermal growth factor receptor, or EGFR. That both defects produce the same outcome may help explain why efforts to treat the disease by targeting only one aberration have faltered.

"Glioblastoma is the most malignant type of brain tumor," said Griffith Harsh, MD, Professor of Neurosurgery at the Stanford University School of Medicine and the study's senior author. Untreated, patients usually survive fewer than six months after diagnosis. After surgical excision, tumors often regrow rapidly. Radiation and temozolomide, a chemotherapeutic agent, can prolong survival, but not by much. These treatments extend median survival to perhaps 18 months.

Defects in NFKBIA, a gene normally present on chromosome 14, have been found in a wide range of cancers including Hodgkin's lymphoma, multiple myeloma, melanoma, and breast, lung and colon cancer. But the new study is the first to implicate the deletion of a copy of NFKBIA as a contributing cause of glioblastoma.

This discovery follows earlier findings that at least one-third of glioblastomas feature an abnormality of the gene coding for EGFR, the cell-surface receptor for the hormone known as epidermal growth factor. In such cases, EFGR is either present in excessive copies or is mutated in a manner that leaves the receptor stuck in the "on" position even when not stimulated by binding to the growth factor. Aberrant EGF receptors continuously send out biochemical signals that direct cells to proliferate, igniting tumor development.

"It's been known for 25 years that EGFR plays a role in glioblastoma as well as many other cancers, and that this gene is aberrantly activated in glioblastoma," said the study's Principal Investigator, Markus Bredel, MD, PhD, who is a Visiting Associate Professor in Stanford's Department of Neurosurgery, Associate Professor at the University of Alabama-Birmingham and Professor of Neuro-oncology at the University of Freiburg in Germany. "We asked ourselves, what causes the majority of glioblastomas that don't have this defect?"

Bredel, Harsh and Branimir Sikic, MD, Professor of Oncology and Clinical Pharmacology at Stanford, had previously found that patients with low NFKBIA expression were resistant to temozolomide treatment. Based on that finding and on hints from other tumor types, Bredel, Harsh and their colleagues at Freiburg and Northwestern University (where most of the work was conducted under Bredel's direction) focused on NFKBIA.

The investigators analyzed several hundred tumor samples collected from glioblastoma patients treated at several institutions between 1989 and 2009, and found NFKBIA deletions in a surprisingly high proportion, 25 percent, of the samples. They also confirmed earlier findings about EGFR, identifying aberrations in that gene in about one-third of these samples. Interestingly, there were only a handful of instances (about 5 percent) where both gene aberrations occurred in the same sample. Thus, the two defects taken together accounted for a majority of all glioblastomas examined.

Moreover, the authors learned, patients with either the NFKBIA or EGFR abnormality had a significantly shorter survival, despite maximal therapy, than the remaining patients (roughly 40 percent) whose tumors bore neither genetic defect.

The defects on NFKBIA and EGFR have a similar effect on an important molecule called NF-kappa-B, a "transcription

factor" found in all cells, but they do this by different mechanisms.

When idle, NF-kappa-B resides in the watery outer region of a cell known as the cytoplasm. But when activated, it heads to the cell's nucleus, where it contacts the cell's genetic material and switches on or off many genes, altering the cell's behavior. In cancer cells, NF-kappa-B can induce proliferation as well as refusal to die under conditions in which even cancer cells would otherwise opt to commit suicide -- for example, when their DNA has been severely damaged by chemotherapeutic agents such as temozolomide.

The biochemical signal sent by overabundant or hyperactive EGFR activates NF-kappa-B, encouraging cancer-cell proliferation and resistance to chemotherapy.

By contrast, NFKBIA codes for a protein called I-kappa-B that inhibits NF-kappa-B. Under normal conditions, I-kappa-B binds to NF-kappa-B and prevents it from moving to the nucleus and altering gene expression. Thus, an NFKBIA deletion, which reduces levels of I-kappa-B in the cell, allows NF-kappa-B to go into overdrive, producing the same proliferative effect as EGFR hyperactivity.

To achieve their findings, the researchers grew glioblastoma cells in culture and used various laboratory methods (such as delivering NFKBIA into the cells via a virus) to increase the activity of I-kappa-B in the cells. They found that doing this in cells with either EGFR hyperactivity or NFKBIA deficiency restored normal appearance and behavior to the cells and made them more vulnerable to temozolomide. But such measures had no effect on glioblastoma cells without either gene abnormality.

The discovery of the role of NFKBIA deletion in glioblastoma, and its dismal effect on survival, has near-term prognostic implications. "The way we identified this deletion for our study is not going to be efficient for general clinical-laboratory use," said Harsh. "But we're trying to develop an improved method -- fast, cheap, reliable. That could happen within a year or so."

The new findings could also have implications for choice of treatment. "If we can determine that a patient's glioblastoma has the NFKBIA deletion, we can target that tumor for treatment with drugs that stabilize I-kappa-B, NFKBIA's protein product," said Bredel. Drugs approved for treating other cancers (for example, bortezomib, for multiple myeloma) or currently under clinical investigation may have that capacity. An early-stage clinical trial of bortezomib for glioblastoma is now under way at Northwestern.

A number of other investigators from several institutions, including Stanford's Hannes Vogel, MD, Professor of Pathology and of Pediatrics, and Bret Mobley, MD, a Clinical Instructor in Pathology, contributed to this study. This work was funded, in part, by Accelerate Brain Cancer Cure, the American Brain Tumor Association, the State of Illinois and a German Cancer Aid Grant.

Markus Bredel, Denise M. Scholtens, Ajay K. Yadav, Angel A. Alvarez, Jaclyn J. Renfrow, James P. Chandler, Irene L.Y. Yu, Maria S. Carro, Fangping Dai, Michael J. Tagge, Roberto Ferrarese, Claudia Bredel, Heidi S. Phillips, Paul J. Lukac, Pierre A. Robe, Astrid Weyerbrock, Hannes Vogel, Steven Dubner, Bret Mobley, Xiaolin He, Adrienne C. Scheck, Branimir I. Sikic, Kenneth D. Aldape, Arnab Chakravarti, Griffith R. Harsh. NFKBIADeletion in Glioblastomas. New England Journal of Medicine, 2010; : 101222140105043 DOI: 10.1056/NEJMoa1006312