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Deleted Gene Worsens Outcomes in Brain CA

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MedPage Today Action Points

- Explain that glioblastoma patients whose brain tumors lack a certain gene appear to have worse outcomes.
- Note that the gene, *NFKBIA* -- an encoding nuclear factor of K-light polypeptide gene enhancer in B-cells inhibitor-alpha -- is an inhibitor of the epidermal growth factor signaling pathway.
- Further note that these findings imply that *NFKBIA*-stabilizing therapies may be effective against glioblastomas that have alterations of EGFR.

Review

Patients with the most common and deadly primary form of brain cancer -- glioblastoma multiforme -- whose tumors are missing a certain gene may have worse outcomes, researchers have found.

A study of almost 800 glioblastoma patients found that deletion of the *NFKBIA* gene had an effect similar to the amplification of epidermal growth factor receptor (EGFR) -- and was also associated with significantly shorter survival than in non-carriers ($P=0.02$), according to Markus Bredel, MD, of the University of Freiburg in Germany, and colleagues.

The findings suggest that "*NFKBIA*-stabilizing therapies may be effective against glioblastomas," Bredel and co-authors reported in the *New England Journal of Medicine*.

Excessive expression of EGFR is one of the molecular hallmarks of glioblastoma. *NFKBIA* -- an encoding nuclear factor of K-light polypeptide gene enhancer in B-cells inhibitor-alpha -- is an inhibitor of the EGFR signaling pathway.

Thus, if the *NFKBIA* gene were deleted, it could contribute to excessive EGFR expression, even in those glioblastomas that do not have alterations of EGFR.

So the researchers looked at 790 human glioblastomas for deletions, mutations, or expression of *NFKBIA* and EGFR from patients treated between July 26, 1989 and Aug. 12, 2009, and compared the molecular results with the outcomes for 570 of the patients.

They found that *NFKBIA* is often deleted -- but not mutated -- in glioblastomas, primarily through the loss of gene copy number, as there were no mutations in

coding or promoter sequences.

The deletion occurs more commonly in nonclassical glioblastomas than in classical disease, they said (32.1% versus 5.9%).

"Which aberration occurs may depend on the tumor's cell of origin and its pattern of accumulation of the other genetic lesions that define glioblastoma subtypes," Bredel and co-authors wrote.

When compared to outcomes, the researchers found that glioblastoma patients missing this gene had outcomes similar to those in patients harboring EGFR mutations.

These outcomes were poor compared with those for patients with normal gene dosages, they added.

Regression analysis showed that patients with two copies of *NFKBIA* survived for significantly longer periods than those harboring a deletion of *NFKBIA* (HR 0.45, 95% CI 0.25 to 0.89, $P=0.02$).

And patients with tumors that had either an *NFKBIA* deletion or EGFR amplification had shorter survival times than those with normal amounts of both (HR 1.69, 95% CI 1.09 to 2.63, $P=0.02$ for *NFKBIA* and HR 1.48, 95% CI 1.02 to 2.13, $P=0.04$ for EGFR).

"Our data support a role for *NFKBIA* in the suppression of glioblastoma tumors," the investigators noted.

The findings imply that *NFKBIA*-stabilizing therapies may be effective against glioblastomas that have alterations of EGFR.

Restoration of the expression of *NFKBIA*, for instance, attenuated the malignant phenotype and increased the vulnerability to chemotherapy of cells cultured from tumors with the deletion, they wrote. Tumor cells became more sensitive to temozolomide, the preferred chemotherapy for glioblastoma.

It also reduced the viability of cells with EGFR amplification, but not of cells with normal gene dosages of both.

"The limited efficacy of molecular therapies targeting EGFR in glioblastomas suggests that the therapeutic effect of EGFR inhibition can be circumvented through cross-coupled signaling from other growth factor receptors that are mutated, amplified, or overexpressed in these tumors," Bredel and colleagues wrote.

"Because *NFKBIA* is a major node downstream of such cross-coupled signaling, therapies that stabilize *NFKBIA* might more effectively restrain oncogenic signaling," they added.

The study was supported by Accelerate Brain Cancer Cure, the Mike Gardner America Brain Tumor Association, German Cancer Aid, State of Illinois, State of Alabama, the National Cancer Institute, Goldhirsch Brain Tumor Research Award, Leach Foundation, Brain Tumor Funders' Collaborative, the Lou Malnati's Cancer Benefit Committee, and the Mazza Foundation.

The researchers reported relationships with Castle Biosciences, Genentech, Roche, and Schering Plough.

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