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Molecular discovery points to new therapies for brain tumors

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A class of brain tumor that tends to emerge in younger patients but is less aggressive than others can be identified by examining DNA methylation of a specific set of genes, scientists at The University of Texas M. D. Anderson Cancer Center and colleagues with The Cancer Genome Atlas report today online at *Cancer Cell*.

The national research group discovered that hypermethylation is a defining aspect of secondary glioblastomas, malignancies that have progressed from lower-grade tumors. Patients with these glioblastomas survive longer after diagnosis than those with other types.

"Discovery of molecular factors that define subgroups of glioblastoma will help us identify new therapeutic options for patients," said study co-senior author Ken Aldape, M.D., professor in the Department of Pathology at M. D. Anderson. "In this case, therapeutically altering the methylation state of the tumor's genes might be a new avenue for treatment."

Altered methylation of DNA in cancer is generally thought to promote tumor development, Aldape said. When methyl groups, consisting of one carbon and three hydrogen atoms, attach to sites called CpG islands in a gene's promoter region, the general result is to shut down the gene, although other factors affect gene regulation. On balance, methylation is thought to have a greater effect in silencing tumor-suppressing genes.

'Remarkably detailed insights into cancer'

Methylation is an epigenetic process; it affects gene expression without damaging or altering the gene's DNA sequence. The Cancer Genome Atlas is a joint initiative of the National Cancer Institute and the National Human Genome Research Institute to increase understanding of cancer genetics.

"Such findings are critical to the detection and treatment of brain cancer based on the genetic or epigenetic profile of each patient's disease," said Francis Collins, M.D., Ph.D., director at the National Institutes of Health. "The depth and breadth of expertise in The Cancer Genome Atlas research network, combined with ever-improving genomic technologies, is generating remarkably detailed insights into cancer."

Gliomas are tumors that form in the astrocytes and glial cells, which support the neurons. They are currently classified by microscopic examination. Glioblastomas, the most aggressive form of brain tumor, account for 50 percent of gliomas and have a median survival time of 15 months.

The team found that 24 of 272 glioblastomas were methylated at CpG islands for the defined gene set, and termed these cases as positive for the CpG island methylator phenotype (CIMP). Subsequent experiments, Aldape said, robustly defined the subgroup by genetic mutation, gene expression pattern and clinical outcome.

Glioblastomas are grouped by several types, or signatures, of gene expression that drive the tumor. Of the 24 methylated tumors, 21 fell in the "proneural" signature in which the genes expressed are associated with neural development. The team found that patients with CpG island methylation had a median age at diagnosis of 36, compared with 59 for those without.

Two avenues to new therapies

Among grade IV glioblastoma patients, the median survival for the CIMP-positive group was 150 weeks, compared with 42 weeks for those negative for this epigenetic alteration. CIMP-positivity was more common in low- and intermediate-grade tumors, with a 10-fold increase in methylation seen in grade II tumors compared with grade IV glioblastomas.

Aldape said study results could lead to better therapies two ways. "First, this alteration could identify glioblastoma patients with outcomes similar to lower grade tumors. Second, since it is so common in lower grade tumors, it represents a new therapeutic target for these patients."

Methylation also was tightly associated with mutation in the IDHI gene in 78 percent of cases. IDHI mutations were recently associated with lower grade gliomas.

The researchers note that a subset of grade IV glioblastoma patients tends to be younger and have a relatively favorable prognosis. These patients might be identified in advance by using biomarkers such as CpG island methylation and IDH1 gene mutations. By the same token, the markers could be used to identify patients with low- or intermediate grade gliomas who may have relatively unfavorable prospects for their tumor grade.

They also found that of the 1,520 genes with promoter hypermethylation, only 293 genes, or 19 percent, showed a decrease in expression. "Epigenetics controls expression potential (of genes), rather than expression state," the authors noted.

Hypermethylation might promote tumor development by silencing two tumor-suppressing genes, the team reported, or by silencing others to

provide a favorable context for genetic damage to occur.

The 27 co-authors on the project are from eight academic institutions and one biotechnology company. "Complex problems, such as defining clinically relevant molecular changes in human cancer, require cooperation among many individuals with complementary expertise and therefore require a 'team science' approach," Aldape said.

Provided by University of Texas M. D. Anderson Cancer Center