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Methylation levels key to glioblastoma survival

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A new study analyzing gene expression among patients with glioblastomas has found that not all of the common, deadly brain tumors appear the same upon closer examination.

The research, directed by scientists at The University of Texas M. D. Anderson Cancer Center, identified three subgroups of tumors that differed according to the degree of overall methylation, or chemical modifications to DNA, finding that patients whose tumors fell in a group with mixed levels of methylation had improved survival time over those with high or low levels of methylation. During methylation, healthy genes can be switched on or off potentially causing cancer without any changes in the underlying DNA sequence.

One group of tumors exhibited extensive methylation, while a second showed very low levels of methylation. In both of these groups, patients fared poorly, with a median survival time of 47 to 54 weeks following diagnosis and a less than 20 percent chance of living beyond two years.

However, a third group of tumors was defined by over- or under-methylation of bits of DNA known as CpG islands. This third, mixed group also showed methylation of a specific set of genes that were unmethylated in the other groups. Patients in this group had a significantly improved overall survival – a median of 99 weeks following diagnosis and a 50 percent chance of living beyond two years.

Results were presented at the American Association for Cancer

Research Molecular Diagnostics in Cancer Therapeutic Development meeting being held here September 22-25.

For the study, researchers analyzed data from 183 glioblastoma patients through the Cancer Genome Atlas, a project organized by the National Cancer Institute and the National Human Genome Research Institute to catalog molecular abnormalities responsible for cancer, using genome analysis techniques. They filtered the data to include the CpG islands that showed a high variation among the samples, resulting in 143 CpG islands, and highlighting the three subgroups of tumors.

Among the 51 genes that were specifically methylated in the mixed group, 14 genes (35 percent) showed a related, greater than 1.5-fold decrease in expression. By comparison, among the 13 genes specifically methylated in the other two groups, three genes (23 percent) showed a related decrease in expression.

Overall, scientists found the mRNA gene expression profile of the mixed group to greatly differ from the others, in particular through an increased expression of genes whose over-expression previously had been found to be associated with improved outcomes, including certain genes associated with neural development. In addition, other genes previously associated with poor outcomes were under-expressed in this group. In all, researchers found more than 200 genes with a higher than 2.5-fold difference in expression between the mixed group versus the other two groups, but minimal gene expression variability between the high and low methylation groups.

"This study shows that the methylation status of CpG islands may serve a robust, and previously unexplored, source of biomarkers for this disease," said lead author Christopher E. Pelloski, M.D., an assistant professor of radiation oncology and pathology at M. D. Anderson. "It also indicates that there seems to be a common theme to glioblastoma

that the more closely the tumor cells resemble cells of neural development, the less aggressive the clinical course; whereas if they more resemble mesenchymal cells, which are poorly differentiated and invasive, the worse the clinical outcome will be.

Source: American Association for Cancer Research