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Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents
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Abstract:

The DNA-repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) inhibits the killing of tumor cells by alkylating agents. MGMT activity is controlled by a promoter; methylation of the promoter silences the gene in cancer, and the cells no longer produce MGMT. We examined gliomas to determine whether methylation of the MGMT promoter is related to the responsiveness of the tumor to alkylating agents. **METHODS:** We analyzed the MGMT promoter in tumor DNA by a methylation-specific polymerase-chain-reaction assay. The gliomas were obtained from patients who had been treated with carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea, or BCNU). The molecular data were correlated with the clinical outcome. **RESULTS:** The MGMT promoter was methylated in gliomas from 19 of 47 patients (40 percent). This finding was associated with regression of the tumor and prolonged overall and disease-free survival. It was an independent and stronger prognostic factor than age, stage, tumor grade, or performance status. **CONCLUSIONS:** Methylation of the MGMT promoter in gliomas is a useful predictor of the responsiveness of the tumors to alkylating agents.

Comments:

Nitrosoureas are widely used as chemotherapeutic agents in the treatment of gliomas. They act by alkylating DNA and causing a cross-link between adjacent DNA strands, ultimately inhibiting cell replication. Inherent repair mechanisms exist that inhibit/reverse DNA cross-linking. One such mechanism is the cellular DNA repair protein O(6)-methylguanine DNA methyltransferase (MGMT), which rapidly reverses DNA alkylation. Although these repair mechanisms are crucial to normal cellular replication, their presence provides resistance to therapies that act via alkylation.² Conversely, attenuation of MGMT increases the sensitivity of tumors to alkylating agents.^{3,4} Although the *MGMT* gene is not commonly deleted, its genetic activity may be altered via methylation of the promotor region.^{1,5} This study by Esteller and colleagues is significant in that it establishes a correlation between the efficacy of nitrosoureas to the methylation state of the promotor region of the *MGMT* gene in gliomas.

Using samples obtained in 47 newly diagnosed gliomas, Esteller and colleagues report that 63% of those in which there was a methylated MGMT promoter had a partial or complete response to the nitrosourea and carmustine, compared with only 4% of those with unmethylated *MGMT* genes. In addition, the median time to disease progression was 21 months in those with methylated *MGMT* genes as compared to only 8 months for unmethylated gliomas. Moreover, the authors offer the methylation status of the MGMT gene as a better predictor of outcome than either the grade of the tumor, Karnofsky Performance Scale status, or the patient's age.

This article was highlighted because it provides new insight into molecular tumor biology as well as offering an explanation for the efficacy, as well as the failure, of chemotherapeutic agents. If true, characterization of the methylation status prior to instituting therapy will help direct the choice of chemotherapeutic agents. Moreover, it may be possible to augment tumor responsiveness by altering the methylation of genes. It is obvious that a better understanding of tumor biological features is needed. However, this article provides promising results in the study of tumor genetics.

References

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