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MGMT promoter methylation across glioma subtypes: biological relevance, treatment response, and survival outcomes

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Abstract

Gliomas are molecularly heterogeneous central nervous system tumors with variable treatment responsiveness and survival outcomes. O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is an important biomarker because it is associated with reduced DNA repair capacity and increased sensitivity to alkylating agents, particularly temozolomide (TMZ). However, its clinical meaning is not uniform across glioma subtypes and should not be interpreted as a universal prognostic marker. In IDH-wildtype glioblastoma, MGMT promoter methylation has the strongest evidence as a predictive biomarker for benefit from TMZ-containing therapy, although survival advantages in treated cohorts should be interpreted mainly as treatment-associated effects unless treatment-independent prognostic value is demonstrated. In IDH-mutant astrocytoma, MGMT methylation may partly reflect IDH-associated global hypermethylation and appears to have limited independent clinical value. In IDH-mutant, 1p/19q-codeleted oligodendroglioma, MGMT methylation may provide supportive, treatment-context-dependent information, particularly in patients receiving alkylating chemotherapy. In pediatric-type and rare molecularly defined gliomas, including histone-altered tumors, MGMT status remains exploratory and should be interpreted alongside methylation class, lineage-defining alterations, tumor location, and treatment history. Technical factors, including assay platform, CpG-site selection, cutoff definition, tissue quality, tumor-cell content, and intratumoral heterogeneity, further complicate interpretation. Because MGMT methylation is biologically continuous, this review further argues that borderline results should be reported as gray-zone or intermediate categories when validated, and that quantitative methylation values should be integrated into subtype-aware multivariable models rather than being reduced exclusively to binary calls. This review summarizes the biological and clinical relevance of MGMT promoter methylation across glioma subtypes and proposes a subtype-aware, treatment-conditional, and assay-aware framework for interpreting its predictive and survival-related significance.

Keywords: Epigenetics; Glioma; MGMT promoter methylation; Treatment response.