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MGMT promoter methylation in malignant gliomas: ready for personalized medicine?

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The DNA repair enzyme O(6)-methylguanine-DNA methyltransferase (MGMT) antagonizes the genotoxic effects of alkylating agents. MGMT promoter methylation is the key mechanism of MGMT gene silencing and predicts a favorable outcome in patients with glioblastoma who are exposed to alkylating agent chemotherapy. This biomarker is on the verge of entering clinical decision-making and is currently used to stratify or even select glioblastoma patients for clinical trials. In other subtypes of glioma, such as anaplastic gliomas, the relevance of MGMT promoter methylation might extend beyond the prediction of chemosensitivity, and could reflect a distinct molecular profile. Here, we review the most commonly used assays for evaluation of MGMT status, outline the prerequisites for standardized tests, and evaluate reasons for difficulties in reproducibility. We critically discuss the prognostic and predictive value of MGMT silencing, reviewing trials in which patients with different types of glioma were treated with various chemotherapy schedules, either upfront or at recurrence. Standardization of MGMT testing requires comparison of different technologies across laboratories and prospectively validated cut-off values for prognostic or predictive effects. Moreover, future clinical trials will need to determine, for each subtype of glioma, the degree to which MGMT promoter methylation is predictive or prognostic, and whether testing should become routine clinical practice.

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