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Extent and Patterns of MGMT Promoter Methylation in Glioblastoma and Respective Derived Spheres.

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Abstract

PURPOSE: Quantitative methylation specific tests suggest that not all cells in a glioblastoma with detectable promoter methylation of the O6-methylguanine DNA methyl transferase (MGMT) gene carry a methylated MGMT allele. This observation may indicate cell subpopulations with distinct MGMT status, raising the question of the clinically relevant cut-off of MGMT methylation therapy. Epigenetic silencing of the MGMT gene by promoter methylation blunts repair of O6-methyl guanine and has been shown to be a predictive factor for benefit from alkylating agent therapy in glioblastoma.

EXPERIMENTAL DESIGN: Ten paired samples of glioblastoma and respective glioblastoma-derived spheres (GS), cultured under stem cell conditions, were analyzed for the degree and pattern of MGMT promoter methylation by methylation specific clone sequencing, MGMT gene dosage, chromatin status, and respective effects on MGMT expression and MGMT activity.

RESULTS: In glioblastoma MGMT methylated alleles ranged from 10 to 90%. In contrast, methylated alleles were highly enriched (100% of clones) in respective GS, even when two MGMT alleles were present, with one exception (<50%). The CpG methylation patterns were characteristic for each glioblastoma exhibiting 25 to 90% methylated CpGs of 28 sites interrogated. Furthermore, MGMT promoter methylation was associated with a non-permissive chromatin status in accordance with very low MGMT transcript levels and undetectable MGMT activity.

CONCLUSIONS: In MGMT methylated glioblastoma, MGMT promoter methylation is highly enriched in GS, which supposedly comprise glioma initiating cells. Thus, even a low percentage of MGMT methylation measured in a glioblastoma sample may be relevant and predict benefit from an alkylating agent therapy.

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