CpG island

CpG islands (or CG islands) are regions with a high frequency of CpG sites. Though objective definitions for CpG islands are limited, the usual formal definition is a region with at least 200 bp, a GC percentage greater than 50%, and an observed-to-expected CpG ratio greater than 60 %.

In each glioblastoma GBM, hundreds of genes are subject to DNA hypermethylation at their CpG island promoters. A subset of GBMs is also characterized by locus-specific and genome-wide decrease in DNA methylation, or DNA hypomethylation. Other epigenetic alterations, such as changes in the position of histone variants and changes in histone modifications are also likely important in the molecular pathology of GBM, but somewhat surprisingly there are very limited data about these in GBM. Alterations in histone modifications are especially important to understand, given that histone deacetylases are targets for drugs that are in clinical trial for GBMs. The technological wave of next-generation sequencing will accelerate GBM epigenome profiling, allowing the direct integration of DNA methylation, histone modification and gene expression profiles. Ultimately, genomic and epigenomic data should provide new predictive markers of response and lead to more effective therapies for GBM [1)].

IDH1/2-mutant gliomas harbor a distinct glioma-CpG island methylation phenotype (G-CIMP) that may promote the initiation and progression of secondary pathway gliomas by silencing tumor-suppressive genes. The potential role of tumor-suppressive microRNAs (MicroRNA; miR) in this process is not understood [2)].

Yin et al. identified a novel hypomethylation signature comprising of three CpGs at non-CpG island (CGI) open sea regions for glioblastomas (GBMs). The hypomethylation signature consistently predicted poor prognosis of GBMs in a series of discovery and validation datasets. It was demonstrated as an independent prognostic indicator, and showed interrelationships with known molecular marks such as MGMT promoter methylation status, and glioma CpG island methylator phenotype (G-CIMP) or IDH1 mutations. Bioinformatic analysis found that the hypomethylation signature was closely associated with the transcriptional status of an EGFR/Vascular endothelial growth factor A/ANXA1-centered gene network. The integrative molecular analysis finally revealed that the gene network defined two distinct clinically relevant molecular subtypes reminiscent of different immature neuroglial lineages in GBMs. The novel hypomethylation signature and relevant gene network may provide new insights into prognostic classification, molecular characterization, and treatment development for GBMs [3)].

Exposure to 1 mg/mL Olea europaea (OLE) caused a significant induction of CpG island methylation in the MGMT gene using Methyl quantitative PCR assay ($P < 0.001$). In WST-1 analysis, the use of 350 μM TMZ plus 1 mg/mL OLE significantly increased the TMZ response of MGMT unmethylated cells ($P = 0.003$). Using the comet assay, the impact of 1 mg/mL OLE plus 350 μM TMZ on the formation of DNA strand breaks was significantly higher than that of 450 μM TMZ alone ($P < 0.001$) and Western blot analysis revealed that, when cells are treated with 1-mg/mL OLE, the total p53 protein levels tended

to decrease. The results presented in this study uniquely demonstrated that OLE synergistically increased the TMZ response of GBM tumors by regulating MGMT gene methylation and p53 expression. However, further studies to validate our findings are required [4].

1)
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