DNMT3A Expression and Hypomethylation as Indicators of Aggressive Genomic Alterations and Poor Outcomes in Lower-Grade Glioma

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Background: Lower-grade gliomas (LGG) exhibit diverse clinical outcomes, with epigenetic alterations increasingly recognized as key drivers of tumor progression. While *DNMT3A* mediates DNA methylation, its specific role as a transcriptional and epigenetic prognostic marker, and its independent associations with genomic alterations in LGG, remains to be fully elucidated.

Methods: We analyzed *DNMT3A* mRNA expression, DNA methylation, and clinical data from the TCGA LGG (PanCancer Atlas) cohort using cBioPortal. We performed independent comparative analyses based on: (1) *DNMT3A* mRNA expression levels (High vs. Low) and (2) DNMT3A DNA methylation levels (Low vs. High). Survival outcomes and the frequencies of Copy Number Alterations (CNAs) in *CDKN2A/B* and *EGFR* were evaluated for each comparison.

Results: High *DNMT3A* expression was significantly associated with shorter overall survival compared to low expression. Similarly, low *DNMT3A* methylation (hypomethylation) showed a trend toward poorer outcomes compared to high methylation. Notably, both high expression and low methylation of *DNMT3A* were consistently associated with a higher prevalence of *CDKN2A*, *CDKN2B*, *CDKN2A-AS1*, and *CDKN2B-AS1* depletions, as well as increased amplifications of *EGFR* and *EGFR-AS1*. These results indicate that both transcriptional and epigenetic activation of DNMT3A serve as indicators for critical genomic instability in LGG.

Conclusions: Our findings suggest that *DNMT3A* acts as a transcriptionally and epigenetically driven prognostic marker in LGG. The independent associations of high expression and low methylation with *CDKN2A/B* loss and *EGFR* amplification highlight *DNMT3A* as a key molecular axis for risk stratification, reflecting a more aggressive genomic landscape in LGG patients.