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Influence of MTHFR rs1801133 (C677T) Polymorphism upon Overall Methylation Levels of Glioblastoma Patients under Inhaled Perillyl Alcohol Treatment

Igor D.P. Soares [1], Giselle M. Faria [2], Marcia R. Amorim [3], Clovis O. da Fonseca [4], Thereza Quirico-Santos [2]*

[1] *Instituto Nacional do Câncer, Centro de Medula Óssea, Divisão de Laboratórios, Laboratório de Células Tronco, RJ, Brasil*

[2] *Departmento de Biologia Celular e Molecular, Instituto de Biologia, Universidade Federal Fluminense, Niterói, RJ, Brasil*

[3] *Departmento de Biologia Geral, Universidade Federal Fluminense, Niterói, RJ, Brasil*

[4] *Departmento de Medicina Especializada , Escola de Medicina, Universidade Federal Fluminense , Niterói, RJ, Brasil*

** Corresponding author: tquirico@id.uff.br*

Abstract

Introduction: Glioblastoma (GBM) are primary brain tumor most common and aggressive in adults, highly proliferative with anabolic pattern and invasiveness. Deleterious genetic changes contribute to tumor agressivenes, low survival, treatment resistance and tumor recurrence. Intranasal administration of the naturally occurring monoterpene perillyl alcohol (POH) has been proven to halts glioma progression and prolongs GBM patients survival. Folate is crucial for biochemical processes with important role on carcinogenesis. MTHFR enzyme controls folic acid metabolic pathway and the balance between DNA synthesis and methylation, influencing global DNA methylation and carcinogenesis.

Aim: To evaluate the influence of *rs1801133* (C677T) functional polymorphism of *MTHFR* gene upon global genomic DNA (gDNA) methylation profile and survival of GBM patients under intranasal therapy with POH.

Material and methods: The study included 100 GBM patients (59 male; 41 female) at terminal stage according the clinical trial approved by Local Ethics Comitee. Genomic DNA from blood leukocytes was used for genotyping assay and global methylation status. Statistical analysis included non parametric tests, Spearman correlation, Chi-squared test, loglinear analysis, Kaplan-Meier analysis and Log-Rank test using SPSS program (version 20.0; 95% of confidence interval; $p<0.05$).

Results and discussion: the majority (73%) showed gDNA with hypomethylation pattern (median = 29.65%), with a significant difference ($p<0.0001$) compared to 27% from hypermethylated group (median = 133.25%). Survival plot of gDNA hypermethylated patients indicated high probability for longer survival, albeit no significat differences between the gDNA methylation beteween groups. Genotyping analysis showed frequencies of 38% for **CC** genotype; 49% for the heterozygous genotype **CT** and 13% for the **TT** genotype. **TT** genotype patients showed a significant ($p=0.037$) and marked reduction on gDNA hypomethylation levels (median = 13.35%) with approximatelly 2.5 fold decrease when compared to **CC** genotype (median = 33.02%). It was also observed a significant, moderate and negative correlation between the **TT** genotype and global gDNA hypomethylation (rho= -0,515; $p=0.006$).Genetic association studies did not found significant association between genotypes and global gDNA hypomethylation. However, it was found individual and significant contribution for the variables **gDNA hypomethylation below 25%** ($p=0,009$; Z score = -2.619), **additive model of contrast** (2TT+CT: $p<0.0001$; Z score = 5.083), **dominant model of contrast** (CT+TT: $p = 0.001$; Z score = 3.439) and **TT** genotype ($p<0.0001$; Z score = - 4.543). The survival plot of **TT** genotype showed high survival probability when compared to the heterozygous (**CT**) and wild type (**CC**) genotypes, but no significant differences were observed between median survival for each genotype of *rs1801133* (C677T), as well as no significant differences of survival times by Log Rank analysis by each genotype.

Conclusion: Even after tumor recurrence, it was possible to identify significant differences in hypomethylation degree among GBM patients, being the **TT** genotype of *rs180133* (C677T) a variable that contributed prominently for DNA hypomethylation pattern. Hypermethylated recurrent GBM patients tend to display a better survival profile, but curiously and controversially, the mutant variants of *rs1801133* (C677T) tends to be related to high survival probability when compared to wild variant which may be related to the efficacy of POH-base therapy.

Keywords:

Polymorphism,

Glioblastoma (GBM),

MTHFR Gene, DNA.