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Impact of MTHFR polymorphisms on methylation of MGMT in glioma patients from Northeast China with different folate levels

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ABSTRACT. Hypomethylation of the O6-methylguanine-DNA-methyltransferase (MGMT) promoter in glioma cells has been associated with temozolomide resistance. S-adenosylmethionine (SAM), which is produced during folate metabolism, is the main source of methyl groups during DNA methylation. As a key enzyme during folate metabolism, polymorphisms of 5,10-methylenetetrahydrofolate reductase (MTHFR) may regulate folate end-products. We investigated the effect of typical polymorphisms of MTHFR (C677T and A1298C) on MGMT methylation based on different serum folate levels in patients with glioma from Northeast China. A total of 275 patients with glioma and 329 without malignant

tumors were tested. Serum folate concentration was assayed by using the electrochemiluminescence immunoassay. MTHFR polymorphisms were detected by Taqman-Fluorescence quantitative polymerase chain reaction (PCR). Methylation-specific PCR was used to assess MGMT methylation. The constituent ratio of glioma patients below the serum folate biological reference value was significantly higher than that of the control population ($P < 0.001$). In patients with oligodendroglioma and glioblastoma, heterozygotes for the A1298C mutation were found in higher frequency than homozygotes or wild types (oligodendroglioma, $P < 0.001$; glioblastoma, $P < 0.01$). When grouped by the median or biological reference value of serum folate, only homozygotes for C677T with low levels of folate were significantly associated with decreased methylation of MGMT (median, $P < 0.001$; biological reference value, $P = 0.036$). These data suggest that, in combination with a negative folate balance in glioma patients, T/T genotypes in MTHFR C677T may be associated with MGMT demethylation.

Key words: Glioma; MGMT; MTHFR; Polymorphisms; Folate

