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MGMT activity, promoter methylation and immunohistochemistry of pre-treatment and recurrent malignant gliomas: A comparative study on astrocytoma and glioblastoma.

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The DNA repair protein O(6)-methylguanine-DNA methyltransferase (MGMT) is a key player in tumor cell resistance. Promoter methylation, MGMT activity and immunohistochemistry are used for determining the MGMT status. However, it is unclear whether MGMT promoter methylation correlates with MGMT activity and whether MGMT promoter methylation of the pre-treatment tumor predicts the MGMT status of recurrences. To address these questions, we determined in pre-treatment and recurrent glioblastomas (GB, WHO IV) MGMT activity, promoter methylation and immunoreactivity. We show that GB that were promoter methylated display a range of 0-62 fmol/mg MGMT, and tumors that were non-methylated 0-423 fmol/mg protein. For astrocytomas (WHO III), promoter methylated samples displayed 0-28 fmol/mg, and non-methylated samples 23-107 fmol/mg. No correlation was found between the intensity of promoter methylation and MGMT activity. Given a threshold level of 30 fmol/mg protein we found a correlation between promoter methylation and no/low MGMT activity in 82.4% of the tumors. This high correlation level was only observed when tumors were excluded showing a hemi-methylated promoter (20%). Therefore, classification of hemi-methylated tumors remains questionable. Further, we show that 39.1% of pre-treatment GB and 5.3% of recurrences were promoter methylated, which is in line with the observed increase of MGMT activity in recurrences. Although individual exceptions were found, the data show an overall correlation between promoter methylation and lack/low MGMT activity in GB and astrocytomas. We also show that promoter methylation assay is superior over immunohistochemistry in determining the MGMT status defined by a given MGMT activity level.

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