O6-Methylguanine-DNA Methyltransferase is a Novel Negative Effector of Invasion in Glioblastoma Multiforme.

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Abstract
The dismal prognosis of glioblastoma multiforme (GBM) is mostly due to the high propensity of GBM tumor cells to invade. We reported an inverse relationship between GBM angiogenicity and expression of the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT), which has been extensively characterized for its role in resistance to alkylating agents used in GBM treatment. In the present study, given the major role of angiogenesis and invasion in GBM aggressiveness, we aimed to investigate the relationship between MGMT expression and GBM invasion. Stable overexpression of MGMT in the U87MG cell line significantly decreased invasion, altered expression of invasion-related genes, decreased expression of α5β1 integrin and focal adhesion kinase, reduced their spindle-shaped morphology and migration compared to the empty vector control. Conversely, shRNA-mediated stable knockdown of MGMT or its pharmacological depletion in the MGMT-positive T98G cell line were required for increased invasion. The inverse relationship between MGMT and invasion was further validated in primary GBM patient-derived cell lines. Using paraffin-embedded tumors from patients with primary newly diagnosed GBM (n= 59), tumor MGMT promoter hypermethylation (MGMT gene silencing) was significantly associated with increased immunohistochemical expression of the pro-invasive matricellular protein SPARC (P= 0.039, chi-square test). Taken together, our findings highlight for the first time the role of MGMT as a negative effector of GBM invasion. Future studies are warranted to elucidate the role of SPARC in the molecular mechanisms underlying the inverse relationship between MGMT and GBM invasion and the potential use of MGMT and SPARC as biomarkers of GBM invasion.

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