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MGMT promoter methylation and hypermutant recurrence in IDH mutant lower-grade glioma

Julie J. Miller and Daniel P. Cahill

Translational Neuro-Oncology Laboratory (J.J.M., D.P.C.), Division of Neuro-Oncology, Department of Neurology (J.J.M.), and Department of Neurosurgery (D.P.C.), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Corresponding Authors: Julie J. Miller, Massachusetts General Hospital, 55 Fruit Street, Yawkey 9E, Boston, MA, 02114. Phone: 617-724-1191; Fax: 617-724-8769 (julie.miller@mgh.harvard.edu); Daniel P. Cahill, Massachusetts General Hospital, 55 Fruit Street, Yawkey 9E, Boston, MA, 02114 (cahill@mgh.harvard.edu).

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Infiltrative lower-grade gliomas (LGGs) are the most common primary brain cancer of younger adults (ages 18–45 y).[1,2] These diffuse gliomas are histological grades II or III within the revised World Health Organization diagnostic classification[3] and harbor mutations in isocitrate dehydrogenase (*IDH*) 1 or 2. They are often initially slow growing and responsive to treatment with surgery and radiation. In addition, adjuvant alkylating chemotherapy has recently been proven effective in lower-grade IDH mutant gliomas, with extended survival demonstrated in international randomized clinical trials combining radiation with the procarbazine/lomustine/vincristine (PCV) regimen[4–6] or oral chemotherapeutic temozolomide (TMZ).[7] Despite this effectiveness, these chemotherapies unfortunately lack durability—recurrences emerge in a substantial fraction of patients, with many cases transforming to a higher-grade tumor arising from malignant subclones that drive lethal disease progression.[8,9] Post-alkylator glioma recurrences can display the mutational signature of an on-target selective pressure of chemotherapy, as escape from DNA damage surveillance can be mediated by mismatch repair–deficient hypermutant genomic evolution.[10–12] This phenomenon is particularly frequent in IDH mutant glioma patients after treatment with TMZ.[13–15] This failure pattern after chemotherapy has motivated research efforts to identify potential biomarkers in pretreatment tumors that could serve as predictors of the eventual development of hypermutation.

In a comprehensive study reported in this issue of *Neuro-Oncology*, Mathur and colleagues present convincing evidence that higher levels of upfront O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and their maintenance through recurrence, are associated with the development of hypermutation in IDH mutant gliomas.[16] They detail the clinical characteristics and hypermutation status at recurrence in 37 TMZ-treated paired cases that were initially diagnosed as LGG. Eighteen of these tumors showed signs of hypermutation at recurrence. Interestingly, when comparing these 18 cases with the 19 non-hypermutant cases, neither age of the patient nor the number of TMZ cycles was related to the development of hypermutation. The investigators then carefully characterized methylation levels in the MGMT promoter region in a quantitative manner using bisulfite amplicon sequencing. They observe that the initial tumor specimen from an eventual hypermutated recurrence generally showed increased methylation levels across cytosine-guanine dinucleotide sites within the MGMT promoter. Most interestingly, for patients who developed hypermutation at recurrence, these methylation levels did not significantly change between initial tumors and recurrences. In contrast, MGMT promoter methylation levels significantly decreased between initial tumors and recurrences for patients who did not develop hypermutation at recurrence. These data suggest that competing mechanistic pathways can mediate escape from selection under TMZ treatment: (i) via unmethylated MGMT promoter and upregulated expression for primary resistance versus (ii) another manifesting hypermutation via mismatch gene repair defects.

All told, the implications of these findings are several. First, while MGMT promoter methylation has a well-established evidence base as a predictor of TMZ responsiveness in high-grade IDH wild-type cohorts,[17,18] these results represent a new and nuanced clinical consideration for MGMT promoter methylation in patients with lower-grade IDH mutant gliomas. These findings suggest that, while MGMT promoter methylation may not predict response to chemotherapy in IDH mutant glioma, it can influence the preferred route by which recurrences arise—tumors with methylated MGMT promoter are more likely to manifest hypermutation at recurrence.

Importantly however, these findings do not predict whether or not a patient would benefit from treatment. Indeed, the emergence of hypermutation is to some extent an indication that the treatment is enforcing a selective pressure on tumor growth, and there exist conflicting data regarding the survival impact of TMZ-induced hypermutation.[14,15] This holds some promise, as these findings raise the possibility that MGMT methylation could be used to select for patients who may benefit from combination therapy in the upfront setting, to minimize the risk

of hypermutant recurrences. To this end, agents such as lomustine (CCNU)[15,18–20] and poly(ADP-ribose) polymerase inhibitors[21–23] have been tested in combination with TMZ, although with some additional toxicity profiles. MGMT methylation profiles may have a role in appropriately allocating patients to such combinations in clinical trials.

Keywords

glioma | IDH1 mutation | temozolomide

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