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The Impact of the DNA-Repair Gene *MGMT* in Malignant Gliomas

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Glioblastoma multiforme (GBM) is the most common and most aggressive primary brain tumor in adults. Despite advances in neurosurgical techniques, radiation and chemotherapy during the past three decades, little progress has been made in the treatment of malignant gliomas and therapy remains mostly palliative. In 2005, the EORTC/CAN-NCIC published the results of a large clinical trial examining the role of adjuvant temozolomide chemotherapy in the management of newly diagnosed GBM [1]. This study defined a new standard therapy for GBM, including maximal surgical tumor resection followed by temozolomide applied concomitantly and adjuvant to local field radiotherapy. This treatment results in a median overall survival time of only 9–15 months from the time of diagnosis [1].

One barrier to successful treatment of malignant glioma is resistance to alkylating agents such as chloroethylnitrosoureas (e.g. carmustine, lomustine, and fotemustine), procarbazine, and temozolomide. The cytotoxic activity of alkylating agents is largely mediated by the formation of O-methylguanine DNA adducts. Consequently, the primary mechanism of resistance is a function of the activity of the DNA repair enzyme O-methylguanine DNA methyltransferase (*MGMT*) in the tumor. The *MGMT* enzyme specifically removes the methyl group from the O⁶ position of guanine, thereby restoring the nucleotide to its native form without causing any DNA strand breaks. Furthermore, *MGMT* is a so-called suicide enzyme, because after the transfer of the alkyl group to an internal cysteine residue in the active site of *MGMT*, the enzyme is irreversibly inactivated, thus requiring de novo protein synthesis to maintain enzyme activity [2].

Epigenetic silencing of the *MGMT* gene by promoter methylation plays an important role in regulating *MGMT* expression [2]. In the last 10 years, several studies identified the *MGMT* promoter methylation status as a potential independent prognostic factor for survival in patients with GBM treated with alkylating agents and its association with a higher rate of clinical response [2]. In a companion tumor biology study to the EORTC/CAN-NCIC clinical trial, Hegi et al. [4] discovered the prognostic impact of the *MGMT* promoter methylation status in patients with newly diagnosed GBM and treated with temozolomide. Furthermore, Martinez et al. [5] comparatively analyzed the *MGMT* promoter methylation status in 186 GBMs from patients with an expected me-

dian survival and 9 from patients with long-term survival. The methylation rate in long-term GBM survivors was significantly higher, suggesting that *MGMT* promoter methylation is a hallmark of long-term survival GBMs and a specific characteristic of this intriguing GBM subtype [5].

In this issue of *Neuroepidemiology*, Zawlik et al. [6] studied the *MGMT* promoter methylation and polymorphisms in 371 GBMs diagnosed at population level. *MGMT* methylation was observed in 44% GBMs, which is in line with data published by Hegi et al. [4]. Interestingly, *MGMT* methylation was observed with a higher frequency in secondary than in primary GBMs (73 vs. 43%). Primary GBMs represent the majority of GBMs (95%), develop rapidly de novo without clinical or histological evidence of a less malignant precursor lesion [7], mainly affect the elderly, and are genetically characterized by loss of heterozygosity 10q, *EGFR* amplification, *p16^{INK4a}* deletion and *PTEN* mutations [7, 8]. Secondary GBMs develop slowly through progression from low-grade diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III) and affect younger patients. In 60% of precursor low-grade astrocytomas, *TP53* mutations are the most frequent and earliest detectable genetic alterations [9]. In this context, Zawlik et al. [6] demonstrate that the frequency of *TP53* G:C→A:T mutations in GBMs with *MGMT* methylation is significantly higher than that in GBMs without *MGMT* methylation. The authors conclude that *MGMT* methylation may be associated with susceptibility to acquire *TP53* mutations. In addition, Zawlik et al. showed that the *MGMT* 143 Val allele in GBMs is significantly less frequent than in a healthy European Caucasian population and is associated with longer survival compared to the *MGMT* 143 Ile allele. Therefore, not only the *MGMT* promoter methylation status, but also *MGMT* polymorphisms may affect the prognosis of GBMs.

The findings reported by Zawlik et al. [6] are of interest to clinical neurooncology for several reasons. First, treatment strategies to overcome *MGMT*-mediated chemoresistance are being actively investigated. Since *MGMT* represents a suicide enzyme inactivated after each reaction, one strategy uses dose-intensified temozolomide schedules to deplete *MGMT* activity in tumor tissue [10]. Several studies have shown that prolonged exposure to temozolomide can deplete *MGMT* activity in blood cells. To date, however, it still remains unclear whether such dose-intensified regimes indeed effectively deplete *MGMT* activity in tumor tissue and whether they are more effective than the standard dosing regimen. Another strategy is the treatment with nontoxic pseudosubstrate inhibitors of *MGMT* (e.g. O⁶-benzylguanine). However, systemic application of *MGMT* inhibitors is limited by an increase in hematologic toxicity [10].

Secondly, in future the optimal treatment for GBM may vary substantially, depending on the *MGMT* expression status, which is in line with the conceptual development of more targeted personalized treatment strategies according to the molecular signatures of GBMs. Such developments are already reflected in the

design of recent clinical trials for GBMs, such as exploring the synergistic effects of the anti-angiogenic drug cilengitide compared to temozolomide monotherapy in patients with methylated GBMs only [11, 12].

Given the central role of MGMT in alkylating agent resistance, MGMT is an ideal potential target for biochemical modulation of drug resistance. This is an area of intense ongoing research, which will hopefully result in further improvements in clinical outcomes.

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