Reference #1

RESEARCH ARTICLE | CANCER

EGFR inhibition down-regulates MGMT and enhances responsiveness to temozolomide in glioblastoma

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Editor's summary

Current treatment for glioblastoma (GBM) includes temozolomide (TMZ), which is more effective when the promoter of O^6 methylguanine DNA methyltransferase (MGMT) is methylated and MGMT expression is repressed. Here, Nayab *et al.* showed that the inhibition of EGFR, an oncogene in GBM, led to the activation of activator protein-1 (AP-1), which repressed MGMT transcription. In addition, concomitant treatment with TMZ and EGFR tyrosine kinase inhibitors (TKIs) did not down-regulate MGMT, potentially explaining the prior failure of clinical trials testing this combination. Pretreatment with EGFR TKIs and subsequent treatment with TMZ, however, were able to down-regulate MGMT and increase sensitivity to TMZ in mouse models of GBM. This work provides a mechanistic framework underlying TMZ resistance and suggests a strategy to optimize GBM treatment. —Amy E. Baek

Abstract

Glioblastoma (GBM) is a devastating cancer with a dismal prognosis. Current treatment includes temozolomide (TMZ), which is more effective in about 50% of GBMs that have O^6-*methylguanine DNA methyltransferase* (*MGMT*) promoter methylation. MGMT is a DNA repair protein that reverses TMZ-induced DNA damage. EGFR is a prime oncogene in GBM. Here, we report that EGFR inhibition induced the down-regulation of MGMT in GBM cells, revealing a previously unidentified link between EGFR signaling and response to TMZ. EGFR inhibition led to activation of two transcription factors, activator protein-1 (AP-1), which repressed MGMT transcription, and nuclear factor κB (NF-κB), which up-regulated *MGMT* transcription. EGFR inhibition also induced AP-1–mediated transcription of miR-616. miR-616 inhibited both MGMT translation and NF-κB activation. Thus, the overall effect of EGFR inhibition was down-regulation of MGMT expression. In addition, we provided an explanation for the prior failure of clinical trials that used concomitant EGFR tyrosine kinase inhibitors (TKIs) and TMZ. TMZ up-regulated MGMT, and concomitant treatment with EGFR TKIs and TMZ failed to down-regulate MGMT. However, pretreatment with EGFR TKIs followed by TMZ efficiently down-regulated MGMT and enhanced TMZ sensitivity in experimental models. Posttreatment tumor tissues from two clinical trials were used to validate these findings. We demonstrated that EGFR inhibitors induced down-regulation of MGMT in posttreatment resected tumor tissues from patients with GBM and the failure of EGFR inhibition to down-regulate MGMT if TMZ was used concomitantly. These data support using EGFR TKIs before TMZ treatment as a therapeutic approach in *MGMT* unmethylated GBM.