Resistance to temozolomide in glioblastoma: role of DNA repair mechanisms

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Glioblastoma (GBM) is an aggressive form of brain cancer with a low survival rate, due in large part to resistance to temozolomide (TMZ), a DNA methylating agent used in combination with radiotherapy as first-line treatment after surgery. The resistance to therapy is a consequence of the action of DNA repair mechanisms that repair the damage caused by an antitumor agent. A role in TMZ resistance has been proposed for high expression of DNA repair proteins such as MGMT, (O6-meG DNA methyltransferase), which directly demethylates O6-meG lesions, or MPG (N-Methylpurine DNA Glycosylase), which repairs N7-meG and N3-meA via Base Excision Repair (BER). However, increased levels of MGMT or MPG only explain a small percentage of cases of tumours resistant to TMZ. Importantly, the most abundant lesion induced by TMZ is N7-meG, which is frequently lost from DNA generating toxic abasic (apurinic/apyrimidinic, AP) sites. Such AP sites are repaired through a pathway initiated either by AP endonucleases or by AP lyases. It is generally assumed that AP endonucleases play a major role, but the contribution of AP lyases to TMZ-resistance in GBM remains largely unknown. Here, we have characterized a panel of GBM cell lines to analyse sensitivity to TMZ and to study the expression of different DNA repair genes. We have found significant differences between TMZ-resistant and TMZ-sensitive GBM cells in the expression levels of some genes involved in AP endonuclease-independent AP site repair. Our results point towards a role of an AP lyase-dependent pathway in the repair of TMZ-dependent damage and may help to identify novel predictive biomarkers and/or therapeutical targets in GBM treatment.