Identification of DNA repair factors involved in resistance of glioblastoma cells to temozolomide

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Glioblastoma (GBM) is an aggressive brain tumour with poor survival rate due, in great part, to resistance to temozolomide (TMZ), the primary chemotherapeutic agent used adjunctively with radiotherapy after surgery. TMZ is an alkylating agent that induces three primary DNA lesions: N7-methylguanine (70%), N3-methyladenine (10%), and O6-methylguanine (7%). Resistance to TMZ has been associated with high expression of DNA repair proteins involved in the repair of these lesions, such as MGMT (O6-meG DNA methyltransferase) or MPG (N-Methylpurine DNA Glycosylase). However, elevated levels of such proteins only explain some cases of TMZ-resistant tumours, suggesting that resistance to this alkylating agent is mediated by several DNA repair pathways. Our aim is to understand the mechanisms used by glioblastoma cells to repair DNA damage induced by TMZ. To achieve this goal, we carried out a transcriptional study of DNA repair genes using PCR arrays in GBM cell lines (A172, T98G, LN229, LN18, U373 and CCF-STTG1) which exhibit different levels of TMZ sensitivity. Out of the 84 genes studied, only DDB2 (DNA damage binding protein 2) showed differences in expression between sensitive and resistant GBM cells. Subsequently, we validated the array results through RT-qPCR and Western blot analysis. Additionally, studies were conducted to examine the expression of DDB2 in GBM cells in response to TMZ treatment. Moreover, we examined whether the expression of DDB2 is regulated by epigenetic mechanisms such as DNA methylation. Our results suggest that DDB2 play a role in the response to TMZ in GBM cells, opening new perspectives to understand the resistance to alkylating agents in tumours.

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