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Sensitivity to temozolomide in glioblastoma: role of epigenetically regulated DNA repair genes

I. Grávalos-Cano[1,2,3]*, A. Muñoz-Fernández[1,2,3], C. Ayala-Roldán[1,2,3], D. Segorbe[1,2,3,] T. Morales-Ruiz[1,2,3], R. R. Ariza[1,2,3], T. Roldán-Arjona[1,2,3] and M.I. Martínez-Macías[1,2,3]

[1] Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Córdoba, Spain
[2] Department of Genetics, University of Córdoba, Córdoba, Spain
[3] Reina Sofía University Hospital, Spain
** ge[2]grcai@uco.es*

Resistance to antitumor therapies is a major problem in the treatment of cancer patients. The resistance to therapy has been correlated, among other causes, with the action of DNA repair mechanisms that remove the damage caused by an antitumor agent. Glioblastoma (GBM) is an aggressive form of brain tumour with a low survival rate, due in large part to resistance to temozolomide (TMZ), a DNA alkylating agent used in combination with radiotherapy as first-line treatment after surgery. A role in TMZ resistance has been proposed for high expression of DNA repair proteins such as MGMT (O6-meG DNA methyltransferase), or MPG (N-Methylpurine DNA Glycosylase). However, increased levels of MGMT or MPG only explain a small percentage of TMZ-resistant tumours. In recent years there has been increasing interest in studying the role that epigenetic silencing of DNA repair genes plays in tumour generation and in antitumor therapy. Indeed, a widely used biomarker to predict response to TMZ in GBM is the MGMT promoter methylation status. A still open question is whether events involving epigenetic silencing in other DNA repair genes, besides MGMT, can be correlated with sensitivity or resistance to TMZ in tumour cells. Here, we have characterized a panel of GBM cell lines by analysing their sensitivity to TMZ. Furthermore, we have examined their capacity of repair TMZ-induced DNA damage, as well as the expression and DNA methylation levels of different DNA repair genes. Our ultimate goal is to contribute to achieve a better knowledge of GMB and facilitate the identification of novel predictive genetic biomarkers and/or therapeutical targets for treatment of this very aggressive tumour.

Keywords:
Glioblastoma, temozolomide sensitivity, BER, epigenetics.