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# MGMT-INDEPENDENT TEMOZOLOMIDE RESISTANCE IN PAEDIATRIC GLIOBLASTOMA CELLS ASSOCIATED WITH A PI3-KINASE-MEDIATED HOX / STEM CELL GENE SIGNATURE.

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### Abstract

Sensitivity to temozolomide (TMZ) is restricted to a subset of glioblastoma patients, with the major determinant of resistance being a lack of promoter methylation of the gene encoding the repair protein DNA methyltransferase MGMT, although other mechanisms are thought to be active. There are, however, limited preclinical data in model systems derived from paediatric glioma patients. We have screened a series of cell lines for TMZ efficacy in vitro, and have investigated the differential mechanisms of resistance involved. In the majority of cell lines, a lack of MGMT promoter methylation, and subsequent protein overexpression, was linked to TMZ resistance. An exception was the paediatric glioblastoma line KNS42. Expression profiling data revealed a co-ordinated upregulation of HOX gene expression in resistant lines, especially KNS42, which was reversed by PI3-kinase pathway inhibition. High levels of HOXA9/HOXA10 gene expression were associated with a shorter survival in paediatric high grade glioma patient samples. Combination treatment in vitro of pathway inhibition and TMZ resulted in a highly synergistic interaction in KNS42 cells. The resistance gene signature further included contiguous genes within the 12q13-q14 amplicon including the Akt enhancer PIKE, significantly overexpressed in the KNS42 line. These cells were also highly enriched for CD133 and other stem cell markers. We have thus demonstrated an in vitro link between PI3-kinase-mediated HOXA9/HOXA10 expression, and a drug-resistant, progenitor cell phenotype in MGMT-independent paediatric glioblastoma.

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