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Effect of aberrant p53 function on temozolomide sensitivity of glioma cell lines and brain tumor initiating cells from glioblastoma.

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Abstract

The most effective chemotherapeutic for glioblastoma (GBM) is the DNA alkylating agent temozolomide (TMZ). In a recent study by Hegi et al. benefit from TMZ was significantly associated with methylation of the promoter of the O6-methylguanine-DNA methyltransferase (MGMT) gene; however, the correlation was imperfect. Some patients with methylated tumors were short survivors and others with unmethylated tumors were long survivors. These exceptions have raised the possibility that TMZ response might be influenced by non-MGMT mechanisms. The effect of p53 status on response to TMZ was explored in traditional glioma cell lines (U87MG, U251MG, U343MG, U373MG, SF767, LN443 and LN2308) and brain tumor initiating cells (BTICs-BT012, BT025, BT042, BT048, BT060 and BT069) in two ways: (1) inhibition of p53 by RNAi and (2) sensitivity in relation to intrinsic p53 status, either wild-type or mutant. Traditional glioma cell lines that did not express a functional p53 were significantly more sensitive to TMZ than cell lines with functionally intact wild-type p53 expression. Altered p53 expression or function had only minor effects on TMZ sensitivity in BTICs and tended to decrease sensitivity to TMZ. RNAi specific for p53 had little effect on sensitivity in p53 null glioma cells. Absence of a functional p53 increases TMZ sensitivity in traditional glioma cell lines, an effect that is independent of MGMT status, and not seen in BTICs. P53 status may influence response to TMZ in differentiated cells in a GBM with a negligible affect on its initiating cells.

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