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Significance of secretory prostate apoptosis response (Par)-4 in drug-induced apoptosis in malignant gliomas

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Glioblastoma (GBM) are grade IV gliomas and are the most common and aggressive of brain tumors in adults. Cancer stem cells (CSC) contribute to chemoresistance in many solid tumors including gliomas. Prostate apoptosis response-4 (Par-4) is tumor suppressor and its function as a pro-apoptotic protein is well documented in many cancers; however, its role in CSC is not well defined. The aim of the study was to investigate the role of Par-4 in drug-induced cytotoxicity using human glioma stem cell (GSC)line- HNGC-2 and primary culture (G1) derived from high grade glioma. The results revealed that of the panel of drugs used - lomustine, carmustine, UCN-01, oxaliplatin, temozolomide and tamoxifen (TAM), only TAM induced apoptosis and up-regulated Par-4 levels significantly. Knock down of Par-4 by siRNA inhibited cell death by TAM, suggesting the role of Par-4 in induction of apoptosis. Mechanistically, TAM-induced apoptosis involved break down of mitochondrial membrane potential, down regulation of Bcl-2 and reduced activation of Akt and ERK 42/44. Secretory Par-4 and GRP-78 were also significantly expressed in GSC on exposure to TAM and specific antibodies to these molecules inhibited cell death suggesting that extrinsic Par-4 is important in TAM-induced apoptosis. Based on these data and our findings that enhanced levels of Par-4 sensitize the resistant GSC to drug-induced apoptosis, we propose that Par-4 may be explored for evaluating anti-tumor agents in CSC.

Notes: