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XRCC3 contributes to temozolomide resistance of glioblastoma cells by promoting DNA double-strand break repair

Wynand Paul Roos, Larissa Frohnapfel, Steve Quiros, Florian Ringel, Bernd Kaina

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Abstract

Glioblastoma is the most frequent and aggressive form of high-grade malignant glioma. Due to the dismal prognosis faced by patients suffering from this disease, there is a need for identifying new targets that might improve therapy. The aim of this study was to determine the contribution of the DNA double-strand break (DSB) repair protein X-ray repair cross-complementing 3 (XRCC3) to the resistance of glioma cells to the chemotherapeutic drug temozolomide. Analysis of a publicly available database, E-GEOD-4290, showed that gliomas overexpress XRCC3 (NM_005432) compared to normal brain tissue. Using an isogenic glioma cell system, in which XRCC3 was downregulated by interference RNA, we demonstrate that XRCC3 protects glioma cells against temozolomide-induced reproductive cell death, apoptosis and cell cycle inhibition. Furthermore, XRCC3 knockdown significantly reduced the rate of repair of DSBs following TMZ treatment, which results in increased drug sensitivity. This study confirms the importance of homologous recombination in the resistance of glioma cells to the methylating drug temozolomide and adds XRCC3 to the list of homology-directed DNA repair proteins as possible targets for therapeutic intervention.