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Rad51 inhibition is an effective means of targeting DNA repair in glioma models and CD133+ tumor-derived cells.

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Abstract

High grade gliomas (HGGs) are characterized by resistance to radiotherapy and chemotherapy. Targeting Rad51-dependent homologous recombination repair may be an effective target for chemo- and radiosensitization. In this study we assessed the role of Rad51-dependent repair on sensitivity to radiation and temozolomide (TMZ) as single agents or in combination. Repair protein levels in established glioma cell lines, early passage glioblastoma multiforme (GBM) cell lines, and normal human astrocytes (NHAs) were measured using western blot. Viability and clonogenic survival assays were used to measure the effects of Rad51 knockdown with radiation (XR) and TMZ. Immunocytochemistry was used to evaluate kinetics of Rad51 and γ -H2AX repair foci. Immunohistochemistry was used to assess Rad51 protein levels in glioma specimens. Repair proteins including Rad51 are upregulated in HGG cells compared with NHA. Established glioma cell lines show a dose-dependent increase in Rad51 foci formation after XR and TMZ. Rad51 levels are inversely correlated with radiosensitivity, and downregulation markedly increases the cytotoxicity of TMZ. Rad51 knockdown also promotes more residual γ -H2AX foci 24 h after combined treatment. Newly established GBM cell lines also have high Rad51 levels and are extremely sensitive to Rad51 knockdown. Clinical samples from recently resected gliomas of varying grades demonstrate that Rad51 levels do not correlate with tumor grade. Rad51-dependent repair makes a significant contribution to DNA repair in glioma cells and contributes to resistance to both XR and TMZ. Agents targeting Rad51-dependent repair would be effective adjuvants in standard combination regimens.

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