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PTEN Loss Compromises Homologous Recombination Repair in Astrocytes: Implications for Glioblastoma Therapy with Temozolomide or Poly(ADP-Ribose) Polymerase Inhibitors.

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Abstract

Glioblastomas (GBM) are lethal brain tumors that are highly resistant to therapy. The only meaningful improvement in therapeutic response came from use of the S(N)1-type alkylating agent temozolomide in combination with ionizing radiation. However, no genetic markers that might predict a better response to DNA alkylating agents have been identified in GBMs, except for loss of O(6-)-methylguanine-DNA methyltransferase via promoter methylation. In this study, using genetically defined primary murine astrocytes as well as human glioma lines, we show that loss of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) confers sensitivity to N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), a functional analogue of temozolomide. We find that MNNG induces replication-associated DNA double-strand breaks (DSB), which are inefficiently repaired in PTEN-deficient astrocytes and trigger apoptosis. Mechanistically, this is because PTEN-null astrocytes are compromised in homologous recombination (HR), which is important for the repair of replication-associated DSBs. Our results suggest that reduced levels of Rad51 paralogs in PTEN-null astrocytes might underlie the HR deficiency of these cells. Importantly, the HR deficiency of PTEN-null cells renders them sensitive to the poly(ADP-ribose) polymerase (PARP) inhibitor ABT-888 due to synthetic lethality. In sum, our results tentatively suggest that patients with PTEN-null GBMs (about 36%) may especially benefit from treatment with DNA alkylating agents such as temozolomide. Significantly, our results also provide a rational basis for treating the subgroup of patients who are PTEN deficient with PARP inhibitors in addition to the current treatment regimen of radiation and temozolomide. Cancer Res; 70(13); OF1-8. (c)2010 AACR.

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