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Functional Antagonism Between Vorinostat and Temozolomide when Combined with Ionizing Radiation (IR) in Glioblastoma

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Background

Glioblastoma is the most common primary adult brain tumor. Surgery followed by radiation therapy in combination with temozolomide (Tmz) produces a median survival of 14.6 months. Tmz is a DNA alkylating agent that leads to the mispairing of guanine residues with thymine. An intact mismatch-repair mechanism (MMR) converts the mispaired thymine into a lethal double-strand DNA break. Vorinostat (SAHA), an HDAC inhibitor, has been shown to act as a radiosensitizer, possibly through inhibition of DNA repair. SAHA has successfully been combined with a number of cytotoxic agents. We hypothesized that SAHA would further potentiate the radiosensitizing properties of Tmz in glioblastoma.

Materials/Methods

Experiments were performed with 2 glioblastoma cell lines (U87, LN18). DNA double strand breaks were quantified by both neutral comet assay and gamma-H2AX immunohistochemistry. Assays were performed immediately, and 24 hours after IR to assess DNA damage and repair respectively. For the neutral comet assay the dose of radiation was 30 Gy and the 'olive moment' was scored. The magnitude of the olive moment correlates with increasing DNA damage. For gamma-H2AX assay, the dose of radiation was 2 Gy and the percentage of cells with more than 3 foci was scored. Quantitative PCR and clonogenic cell survival were performed using standard techniques.

Results

In the absence of drug, radiation induced DNA-double strand breaks were almost completely repaired within 24-hours. In U87 both Tmz + IR, and SAHA + IR increased the olive moment compared to IR alone (24 hour post IR time-point). When Tmz and SAHA were combined together with IR, the olive moment decreased to 6.5 as compared to Tmz + IR alone 8.7 ($p < 0.05$). Similarly, in the absence of IR, SAHA was found to decrease Tmz induced DNA damage. Comparable results were obtained with gamma-H2AX assay and with the LN18 cell line. Clonogenic radiation survival assay demonstrated Tmz + SAHA to be no more effective than Tmz alone in potentiating the cytotoxic effect of IR. On qPCR, SAHA was found to down-regulate MLH1, MLH3, MSH2 and MSH 3, key genes involved in MMR.

Conclusion

Both Tmz and SAHA individually potentiated the effect of IR, inhibiting the repair of DNA double strand breaks. However, when cells were exposed to both drugs together less DNA damage was seen than with Tmz alone. Based upon qPCR data we hypothesize that SAHA down regulates the MMR pathway. Our work demonstrates that the addition of an HDAC inhibitor to cytotoxic agents may produce unexpected antagonism.

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