Dual inhibition of BER by TRC102 and PARP inhibitor (ABT 888) synergistically enhances cytotoxicity of TMZ in human melanoma

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Abstract

Malignant melanoma, the most fatal skin cancer, has increased in incidence by 5-fold in the past 40 years, the fastest rate increase of any human malignancy. This disease metastasizes rapidly and is highly resistant to chemotherapy and other treatments. Currently, temozolomide (TMZ) is an important part of treatment regimens for advanced metastatic melanoma. However, drug resistance often occurs in treatment failure. A major resistance factor to the presence of elaborate mechanisms of DNA repair. We have previously studied the role of base excision repair (BER) in conferring TMZ resistance and explored a combined therapy by targeting BER with methoxamine (TRC102), an inhibitor of BER, which binds to abasic sites and disrupts the BER pathway. The potential of TMZ by TRC102 has been validated in different tumor types in vitro and in xenograft models. Results showed TRC102 potentiates of TMZ was accompanied by a remarkable induction of DNA strand breaks. In this study, we examined the therapeutic efficacy of the combination of TMZ with TRC102 and a PARP inhibitor (ABT888) in three melanoma cell lines (A375, WM9, and WM164) and in melanoma xenografts. PARP, an enzyme critical in BER pathway, is actively involved in the repair of DNA single and double strand breaks. We hypothesized the inhibition of PARP would inhibit BER with the accumulation of large numbers of unrepaired DNA strand breaks and the combination of TRC102 and ABT888 would synergistically enhance the anti-tumor effect of TMZ through dual inhibition of BER. Results showed that compared to TMZ alone, the combination with either ABT888 or TRC102 more effectively inhibited cell viability and induced apoptosis in A375 and WM9, but not in WM164 melanoma cell lines. The resistance in WM164 cells is probably related to a deficiency in methylpurine-DNA glycosylase, which is responsible for removing TMZ-induced methylated DNA adducts (N7mG and N3mA) and producing toxic AP sites. When combined with TMZ and TRC102, ABT888 at a concentration of 5 µM efficiently potentiated the combination with either ABT888 or TRC102 more effectively inhibited cell viability and induced apoptosis in A375 and WM9 melanoma cell lines, respectively, and 4 fold in WM164 cells. Cytotoxicity was correlated with the induction of unrepaired DNA strand breaks and the combination of TRC102 and ABT888 would synergistically enhance the anti-tumor effect of TMZ through dual inhibition of BER.

Hypothesis: The inhibition of PARP would block BER with the accumulation of large numbers of unrepaired DNA strand breaks and the combination of TRC102 and ABT888 would synergistically enhance the anti-tumor effect of TMZ through dual inhibition of BER.

Results

PARP inhibitor (ABT888) potentiates TMZ cytotoxicity in human melanoma xenografts

Background

Base excision repair pathway in processing of TMZ damage

PARP inhibitor (ABT888) enhances TMZ and TRC102 cytotoxicity in melanoma cell lines

PARP inhibitor (ABT888) enhances TMZ and TRC102 cytotoxicity in melanoma cell lines

Summary

• PARP inhibitor (ABT-888) enhances cytotoxicity of the combination of TRC102 and TMZ in human melanoma cell lines and xenografts due to accumulation of unrepaired DNA strand breaks
• PARP inhibitor (ABT-888) has no toxicity alone or in combination with TRC102