Synthetic Enhancement of Temozolomide Sensitivity in MSH6-Deficient Glioblastoma Stem Cells by Poly (ADP-Ribose) Polymerase 1 Inhibition

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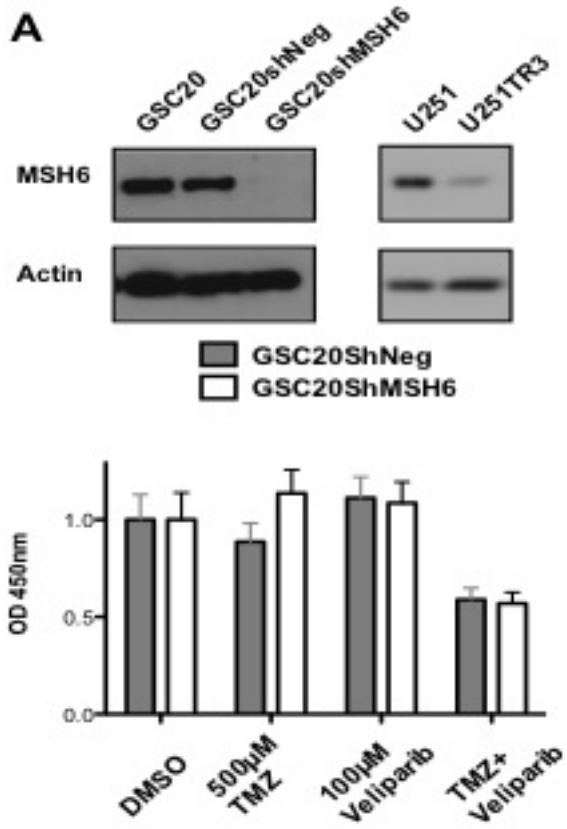
Introduction

Glioblastoma, the most common primary brain tumor, is often initially responsive to alkylating chemotherapeutic-containing regimens, but invariably these tumors return with few effective therapeutic options. Emergence of mismatch repair (MMR) pathway deficiency via MSH6 inactivation in post-alkylator glioblastomas has been established as a significant mechanism of treatment resistance.

Methods

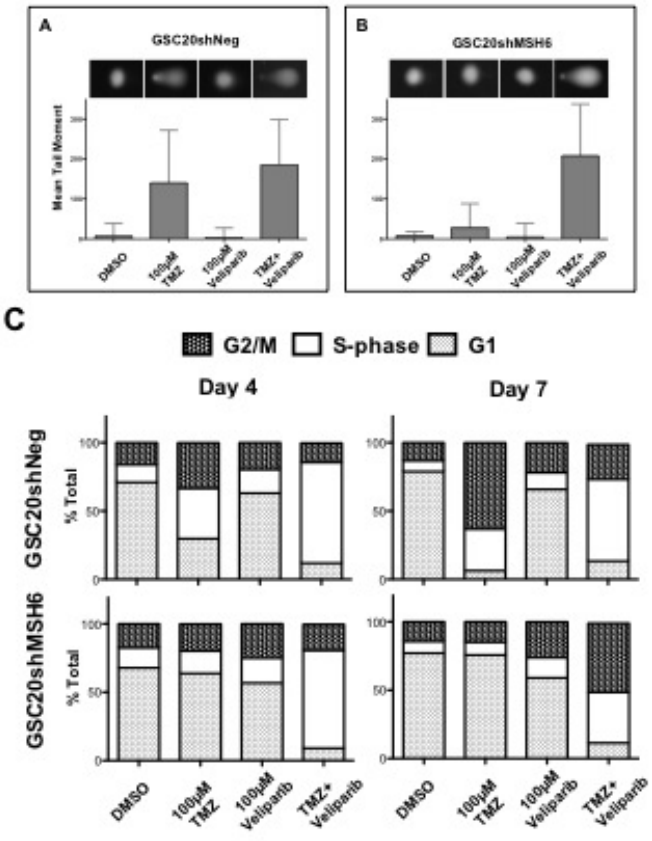
Here, we examine the susceptibility of MSH6-mutated glioblastoma lines and MSH6-inactivated glioma stem cell lines to treatment with the alkylating chemotherapeutic agent temozolomide (TMZ) paired with the poly (ADP-ribose) polymerase 1 (PARP) inhibitor veliparib (VPB, also known as ABT-888), a combination that is currently in phase II clinical trials.



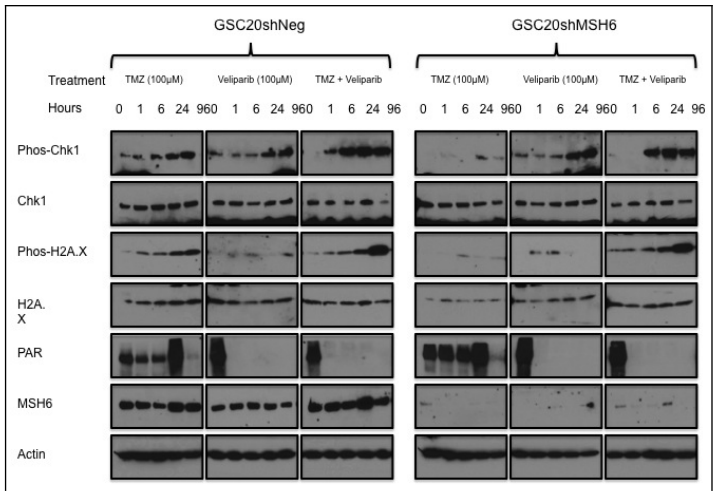
Development of GSC20shMSH6 stem cell line shows TMZ resistance and sensitivity restoration with addition of Veliparib.

Results

We show that addition of VPB restores TMZ sensitivity in these previously TMZ-resistant lines in an MSH6-specific manner (termed “synthetic enhancement”). We further show that combination therapy can prevent the emergent outgrowth of MSH6 mutant stem cells, and thus can close off this treatment escape pathway at its potential source. Recovery of tumor cell sensitivity is associated with re-accumulation of phosphorylated Chk1 and phosphorylated H2AX eventually leading to DNA breaks, indicating restoration of a common mechanistic pathway of treatment effect.



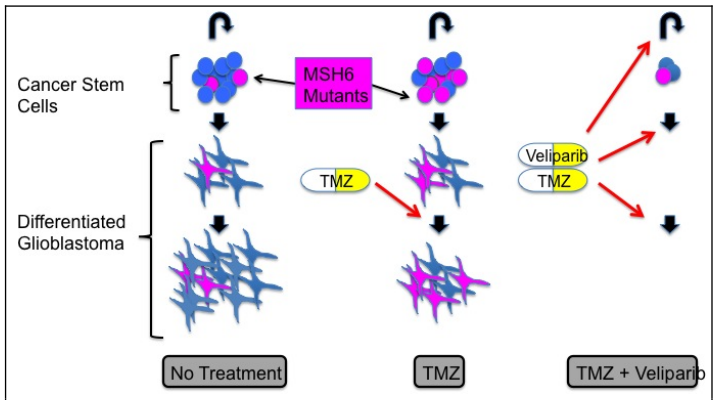
A Mechanistic Analysis shows combination TMZ and VPB therapy restores synthesis arrest, G2/M checkpoint activation, and DNA breaks in MSH6 mutant lines.



Addition of Veliparib inhibits the BER pathway causing accumulation of cell cycle checkpoint proteins phos-Chk1 and phos-H2A.X

Conclusions

These results identify a genetically-defined subgroup of MSH6 deficient recurrent glioblastomas which may benefit from targeted combination therapy with TMZ and VPB. TMZ and VPB therapy can be effective for both differentiated glioblastoma and GSCs. The efficacy of therapy in both populations is likely to be essential for obtaining a lasting response without the development of a chemoresistant population.



Combination TMZ and VPB therapy prevents emergence of TMZ resistant MSH6 mutant subpopulation