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Exploring Potential Strategies Overcoming the PARPi Resistance in an Olaparib-Induced MDA-MB-436 Resistant Model

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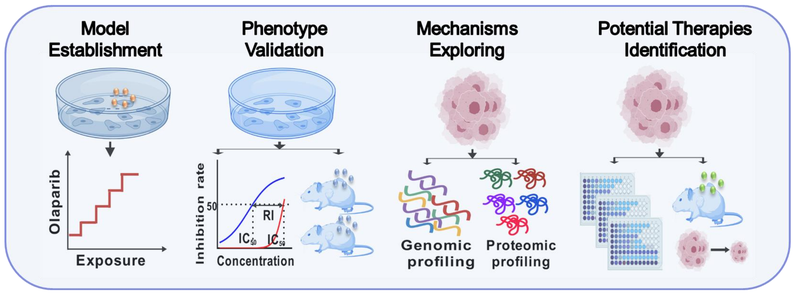
Introduction

Poly (ADP-ribose) polymerase inhibitors (PARPi) have emerged as a promising therapeutic approach in the treatment of various cancers, particularly those with deficiencies in DNA repair mechanisms. However, the clinical efficacy of PARPi is often limited by the development of resistance, which poses a significant challenge to their long-term use. Elucidating the molecular mechanisms underlying PARPi resistance is crucial for developing novel therapeutic agents and strategies to overcome this resistance and optimize patient treatment regimens.

In this study, we established an olaparib-resistant MDA-MB-436 breast cancer cell model with robust resistance to olaparib, which was validated both *in vitro* and *in vivo*. Notably, the olaparib-resistant MDA-MB-436 cells exhibited cross-resistance to other PARP inhibitors, as well as reduced sensitivity to cisplatin compared with parental MDA-MB-436 cells. The clear resistance mechanism and its clinical value remain to be further illuminated.

In summary, our olaparib-resistant MDA-MB-436 model will enhance the understanding of underlying resistance mechanism and aid in exploring the potential strategies that might overcome the resistance such as combinatorial therapies and next-line targeted therapies.

Experimental Design



Generation of Olaparib induced resistant MDA-MB-436 model. MDA-MB-436 cells were continuously exposed to stepwise-increasing concentrations of Olaparib. Resistance phenotype was validated through cell viability assay and xenograft study. RNA profiling was conducted to elucidate the drug resistance mechanisms, and targets of interest were validated through qPCR/WB. Potential therapeutic strategies for overcoming resistance were assessed using both *in vitro* cell viability assays and *in vivo* tumor model studies. Figures were created with *BioGDP.com.*

Results

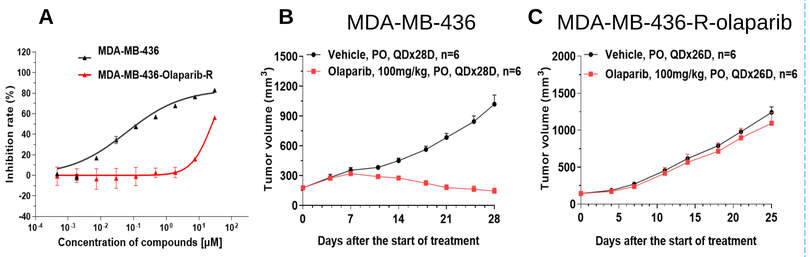


Figure 1. Validation of induced MDA-MB-436-R-olaparib cells. The response of parental MDA-MB-436 cells and MDA-MB-436-R-olaparib cells to Olaparib were assessed through (A) *in vitro* cell viability assay; (B) and (C) *in vivo* xenograft study.

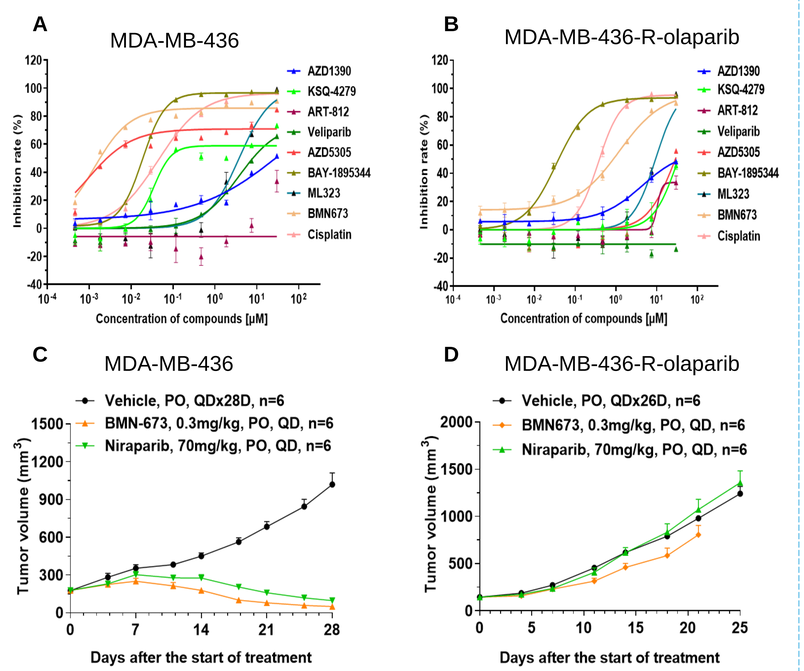


Figure 2. MDA-MB-436-R-olaparib model showed cross-resistance to other PARP inhibitors. (A) and (B) *In vitro* cell viability assays on MDA-MB-436 and MDA-MB-436-R-olaparib cells. (C) and (D) *In vivo* efficacy of PARPi on MDA-MB-436 and MDA-MB-436-R-olaparib tumor xenograft models.

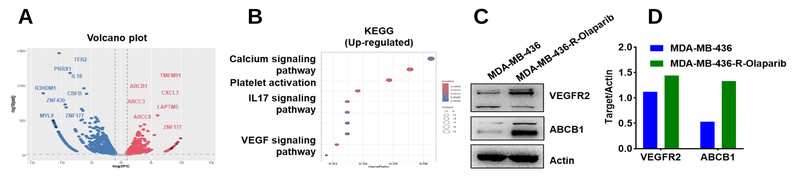


Figure 3. Exploring the mechanisms behind olaparib resistance. (A) Volcano plot of differentially expressed genes in RNA-seq. (B) KEGG enrichment of up-regulated signaling pathways in MDA-MB-436-R-olaparib cells. (C) and (D) Western blot and quantification of VEGFR2 and ABCB1 in MDA-MB-436-R-olaparib cells.

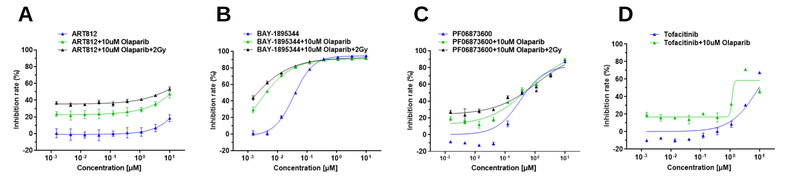


Figure 4. Combinatorial strategies to overcome olaparib resistance. (A), (B), (C), and (D) *In vitro* CTG analysis of MDA-MB-436-R-olaparib cells treated with POLQ inhibitor (ART812), ATR inhibitor (BAY-1895344), CDK2/4/6 inhibitor (PF06873600), and JAK inhibitor (Tofacitinib) in combination with Olaparib alone or combined with Radiation therapy.

Conclusion

We developed an olaparib-resistant MDA-MB-436 model exhibiting cross-resistance to PARP inhibitors (PARPi), independent of BRCA1/2 reversion mutations. Bioinformatic analysis revealed that resistance may involve multiple genes and pathways (e.g., ABCB1 drug efflux pump, VEGF-mediated angiogenesis), providing clues for further investigation. *In vitro* cell viability assays demonstrated enhanced sensitivity of resistant cells to other targeted therapies or radiotherapy when combined with Olaparib. This study provides insight into the development of novel combinatorial therapies and next-generation PARP inhibitors to overcome PARPi resistance.

References

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2. Dias MP, Moser SC, Ganesan S, Jonkers J. Understanding and overcoming resistance to PARP inhibitors in cancer therapy. *Nat Rev Clin Oncol*. 2021 Dec;18(12):773-791.

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