Multi-omics Profiling of Olaparib Resistance in Ovarian Cancer and AI-Driven Discovery of Reversal Therapeutics

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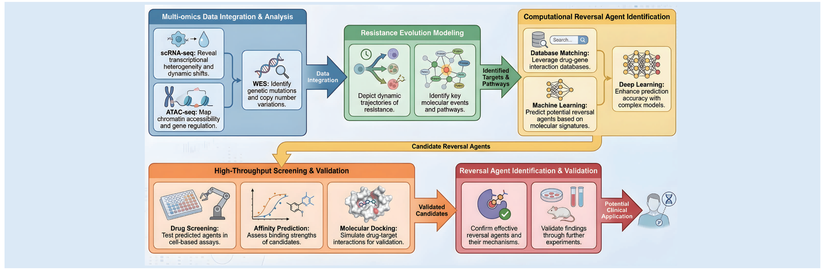
Introduction

Poly (ADP-ribose) polymerase inhibitors (PARPi), such as Olaparib, have revolutionized the targeted treatment of ovarian cancer. However, the emergence of acquired drug resistance significantly limits their long-term clinical efficacy. The molecular mechanisms driving Olaparib resistance are highly heterogeneous, involving dynamic cellular state transitions and complex multi-level regulations that cannot be fully captured by bulk profiling alone. In this study, we established a comprehensive multi-omics integration framework (scRNA-seq, ATAC-seq, WES, and bulk RNA-seq) to delineate the evolutionary trajectory and chromatin regulatory landscape of Olaparib-resistant ovarian cancer cells. Furthermore, we developed an AI-driven drug screening pipeline integrating machine learning feature extraction and deep learning affinity prediction to identify potential reversal agents. This study provides a systematic multi-dimensional map of PARPi resistance and offers a reliable translational workflow for discovering synergistic combination therapies.

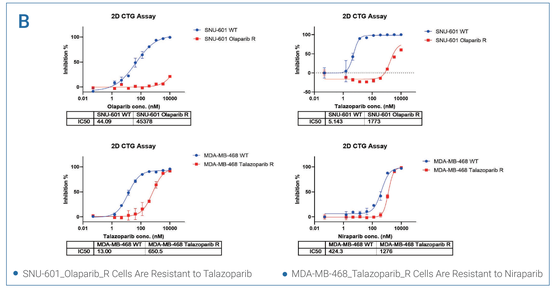
Integrative Multi-omics and AI-driven Framework for Reversing Olaparib Resistance



A

Resistant cell lines
HCC1806 Talazoparib R
HCC1806 Niraparib R
HCC1806 Olaparib R
MDAMB468 Talazoparib R
MDAMB468 Olaparib R
SNU601 Olaparib R
NCIH460 Paclitaxel R
A2780 Olaparib R
A2780 Cisplatin R
PANC1 Talazoparib R

B



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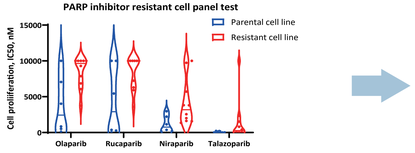

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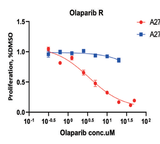
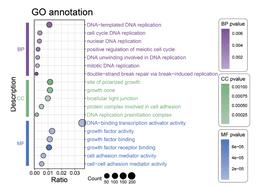


Figure 1. Drug-resistant cell line. A. DDR-associated drug-resistant cell lines; B. Detection of drug-resistant cell line IC50; C. Comparison between drug-resistant cell line IC50 and wild type;D.Construction of typical drug-resistant cell line A2780-OR.

RNA-seq reveals the remodeling of key drug resistance pathways

A



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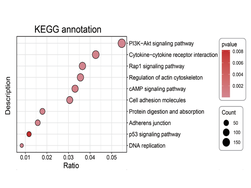
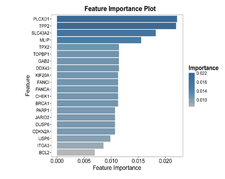


Figure 2. Enrichment of RNA-seq differential gene pathway. A .GO pathway enrichment; B.KEGG pathway enrichment.

Computer-aided drug screening

A



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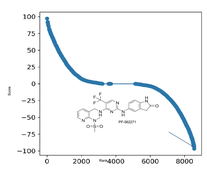

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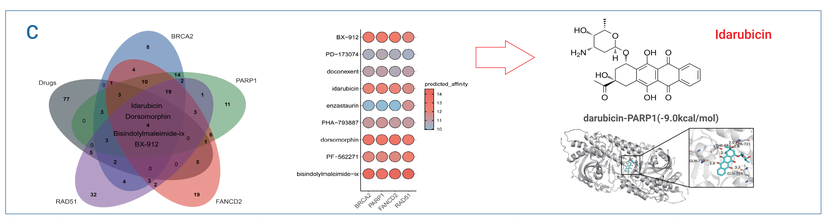
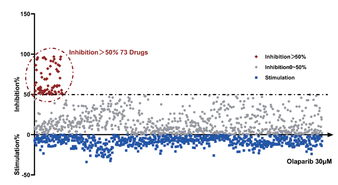


Figure 3. Computer-aided drug screening. A.Distribution of drug prediction scores in cMAP database; B. Distribution of drug prediction scores in cMAP database; C.Prediction of drug targets in GAT_GCN network.

Screening and confirmation of Qualcomm quantity in 'wet experiment'

A



Drug	Cas.NO	Disease	Reported Target
Idarubicin	HY-17381	leukemia	Topoisomerase II
Omaveloxolone	HY-12212	Inflammation	Nrf2/NF-κb pathway
Dipyrithione	HY-N8432	Dermatomycosis	Apoptosis
Triptonide	HY-32736	lymphoma/Inflammation	Wnt pathway
Bardoxolone methyl	HY-13324	Neuropathic pain/COVID-19	Nrf2 pathway

B

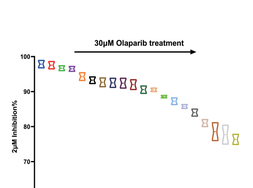


Figure 4. Echo Qualcomm dose medicine.A.Screening of MCE-FDA drug library; B.The screened drugs with Top scores.

Phenotypic verification of combined medication

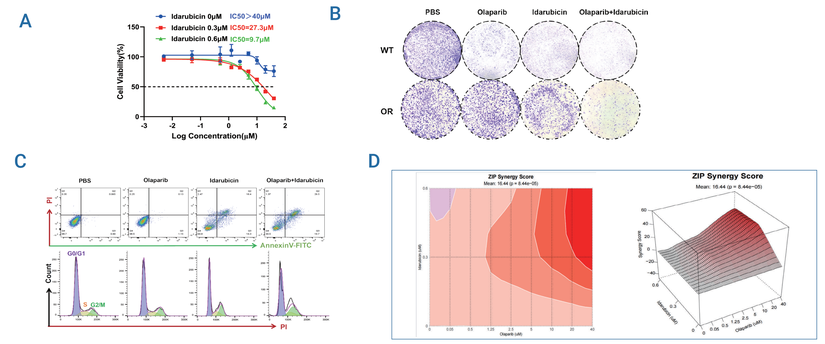


Figure 5. Inhibition of tumor progress by combined drugs. A.Olaparib IC50 under different doses of Idarubicin; B. Colony formation under different drug treatments treatment;C.Cell cycle and apoptosis were detected by FACS;D.SynergyFinder+ Computing Combined Efficiency.

Molecular mechanism of reversing drug resistance

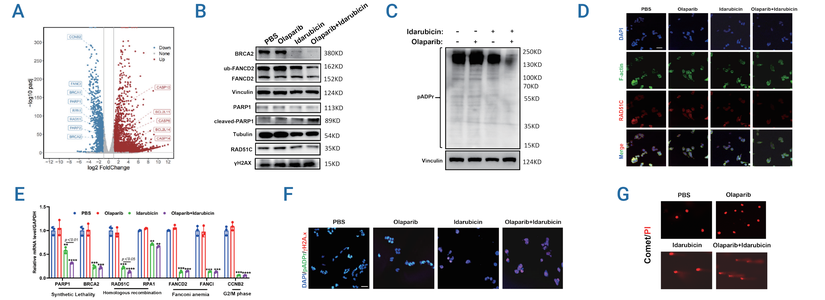


Figure 6. Molecular mechanism of reversing drug resistance. A.RNA-seq after Idarubicin treatment; B.DDR pathway WB detection;C.PADPr enzyme activity WB; D.Detection of DDR protein IFA; E. QPCR detection of DDR key genes; F.γH2A.x co-location IFA; G. Detection of DNA damage by comet assay.

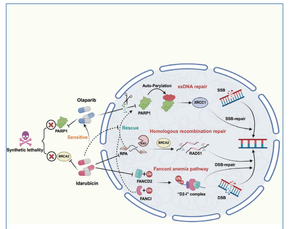


Figure 7 Schematic diagram of molecular mechanism of Idarubicin reversing drug resistance.

Summary

Through multi-omics profiling, we revealed that Olaparib resistance in ovarian cancer is a dynamic evolutionary process driven by hyperactivated DNA repair mechanisms. By integrating an AI-guided computational pipeline with high-throughput screening of 1960 compounds, we identified Idarubicin as a potent resistance-reversal agent. Mechanistically, Idarubicin synergizes with Olaparib by suppressing HR/FA repair pathways, which amplifies DNA double-strand breaks and successfully restores synthetic lethality in resistant cells, providing a promising combination therapeutic strategy for clinical application.