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PELP1 inhibition disrupts DNA repair and enhances topoisomerase inhibitor efficacy in triple-negative breast cancer

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Introduction

Triple-negative breast cancers (TNBCs) account for a sizable portion of breast cancer deaths (15–24%) and are characterized by a more aggressive clinical course, a worse prognosis, and a higher propensity to metastasize. Proline-, glutamic acid-, and leucine-rich protein 1 (PELP1) is an oncogene that plays a critical role in TNBC progression. PELP1 expression is deregulated in TNBC, and its status is a prognostic indicator of poor TNBC survival. Recently, a small molecule inhibitor of PELP1 (SMIP34), which binds to and degrades PELP1, was developed. This proposal aims to identify a novel combination therapy using SMIP34 and pave the path for a novel combination therapy.

Methods

We used multiple TNBC cell lines, PELP1 inhibitor SMIP34 and 140 FDA-approved medications in combination with SMIP34 in this study. Effect SMIP34 combination therapy on cell survival was measured using MTT and colony formation, and Annexin V based apoptosis assays. Mechanistic studies were done using RT-qPCR, western blotting, immunoprecipitation, proximity ligation and mass spec assays, reporter genes assays, immunofluorescence, and comet assays. The utility of SMIP34+TI combination therapy was evaluated using MDA-MB-231 xenografts, and patient-derived organoids (PDOs).

Key findings

- Development of IPTG-inducible PELP1 KD TNBC cells
- PELP1 KD or pharmacological inhibition reduced the clonogenicity under conditions of DNA damage
- FDA drug screen identified that PELP1 inhibition is synergistic to topoisomerase inhibitors
- PELP1 KD or pharmacological inhibition enhanced DNA damage measured by the comet assay
- Western blotting and phospho-antibody arrays revealed upregulation of DDR and checkpoint proteins, including γ-H2AX, p-CHK2, p-ATR, p-CHK1, p-BRCA1, and p21, indicating enhanced replication stress and cell cycle arrest.
- SMIP34 combination therapy with a topoisomerase inhibitor significantly reduced the growth of TNBC Xenografts compared to monotherapy

Conclusions

Our results indicate that the efficacy of topoisomerase inhibitors is improved by the inhibition of PELP1. Combining a topoisomerase inhibitor with a PELP1 inhibitor may serve as a novel targeted therapy for the treatment of TNBC.

References

Altwegg KA, et al. A First-in-Class Inhibitor of ER Coregulator PELP1 Targets ER+ Breast Cancer. Cancer Res. 2022 Oct 17;82(20):3830-3844. doi: 10.1158/0008-5472.CAN-22-0698. PMID: 35950923; PMCID: PMC9588738.

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