USP1 inhibitor synthetic lethality in BRCA1/2-mutant cancer is driven by PCNA ubiquitination

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Abstract

CRISPR-based functional genomic screening is a powerful approach for identifying novel classes of synthetic lethal drug targets. Here, we define the drug-discovery pipeline USP1 as a synthetic lethal target in cancers with underlying DNA repair vulnerabilities. A high-throughput and sensitive small molecule USP1 inhibitor confirmed a synthetic lethality defect in BRCA1-mutant, but not WT cell lines by blocking replication stress-induced apoptosis. USP1 dependency was enhanced upon replication stress-mediated DNA damage, highlighting a functional connection between USP1 stabilization and cell death. Post hoc test, comparing treatment conditions against DMSO control, ****

et al., 2017). BRCA1 reversion was confirmed by immunoblotting and sequencing. (C) Dose response of indicated USP1 dependency is mediated by PCNA ubiquitination and consequent PCNA protein loss SD.

In vitro assays were performed in BRCA1 mutant Activity of USP1i in SD. (D) DUB (deubiquitinating enzyme) panel profiling of TNG USP1i at 10 µM using Ubiquigent USP1i and Characterization of USP1 inhibitors representative of Tango lead SEM.

In vivo USP1 is synthetic lethal in BRCA1/2 mutant tumors

USP1 inhibition induces replication stress and DNA damage

USP1 inhibition is synergistic with PARPi inhibitors

Summary

- USP1 is synthetic lethal in BRCA1/2 mutant tumors
- USP1 dependency is mediated by PCNA ubiquitination and consequent PCNA protein loss
- CRISPR knockout of RAD14-I/UBE2A and UBE2C, but not PARPi resistance gene, rescue PCNA sensitivity
- USP1 inhibitors are synergistic in BRCA1/2 mutant tumors
- Tango lead series USP1 inhibitors are highly potent and selective
- In vitro selectivity against BRCA1 mutant and PARPi sensitive cell lines
- In vivo single agent and combination activity against multiple BRCA1/2 mutant xenografts
- A subset of BRCA1/2 WT lung cancer cell lines are sensitive to USP1i, representing additional patient oncogene opportunities

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