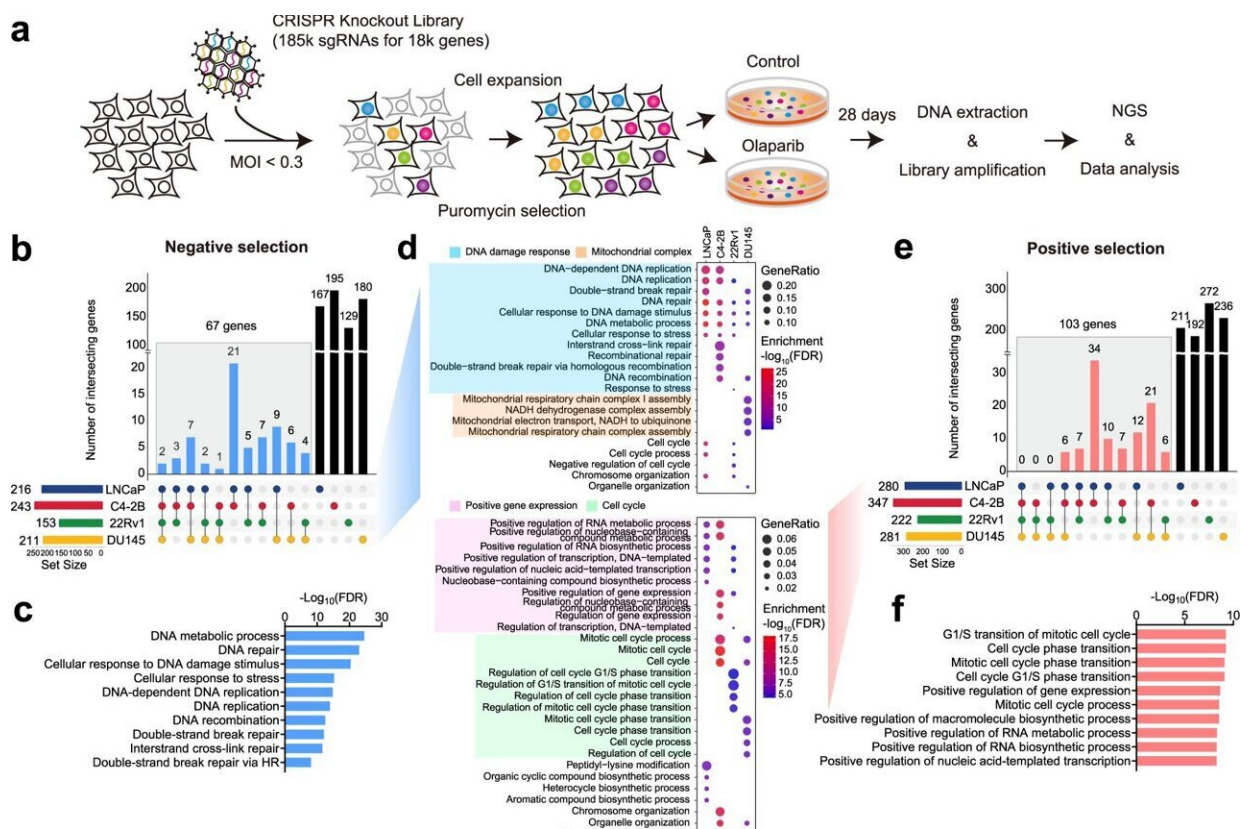# Genome-wide CRISPR screens identify PARP inhibitor sensitivity and resistance in prostate cancer

April 4 2023

CRISPR screens identify genes that modulate PARPi response in PCa cells. a Schematic of genome-wide CRISPR/Cas9 screens. b UpSet plot of negatively selected genes in four PCa cell lines as indicated. Blue bars indicate the number of common hits in at least two screens. c Top GO terms enriched in 67 common hits from negative selection. d Top GO terms enriched in negatively (upper panel) and positively (lower panel) selected genes in each individual cell line. e

UpSet plot of positively selected genes in four PCa cell lines as indicated. Red bars indicate the number of common hits in at least two screens. f Top GO terms enriched in 103 common hits from positive selection. g The networks of common hits from negative selection grouped according to their roles in specific pathways and their genetic and physical interactions (gray lines) based on STRING analysis. h The networks of common hits from positive selection, grouped as in (g). i Top-ranked genes from CRISPR screens determined by comparing olaparib to DMSO treatment. Genes are ranked by the average of differential β-scores from all four cell lines. Negatively and positively selected genes are marked in blue and red, respectively. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-35880-y

Prostate cancer tumors harboring BRCA1/2 mutations are exceptionally sensitive to PARP inhibitors, while genomic alterations in other DNA damage response (DDR) genes are less responsive. To identify previously unknown genes whose loss has a profound impact on PARP inhibitor response, researchers from Dana-Farber Brigham Cancer Center led a multinational effort to perform genome-wide CRISPR-Cas9 knockout screens. The study goal was to inform the use of PARP inhibitors beyond BRCA1/2-deficient tumors and support reevaluation of current biomarkers for PARP inhibition in prostate cancer.

The findings are published in the journal *Nature Communications*.

The study identified multiple novel genes (e.g., MMS22L and RNASEH2B) that are frequently deleted in [prostate cancer](link). These genes could serve as predictive biomarkers for PARP inhibitor response in prostate cancer, according to the study. The research team also found that loss of CHEK2 (the FDA-approved biomarker for therapeutic response to olaparib) confers resistance, rather than sensitivity, to PARP inhibition.

"Current targeted cancer therapies, including PARP inhibitors, are largely guided by mutations of a single gene and overlook concurrent genomic alterations," said Li Jia, Ph.D., director of Urology Research, Brigham and Women's Hospital. "We found that PARP inhibitor sensitivity instead may depend on interaction between multiple genomic alterations. Therefore, comprehensive genomic analysis may help improve clinical decision making."

More information: Takuya Tsujino et al, CRISPR screens reveal genetic determinants of PARP inhibitor sensitivity and resistance in prostate cancer, *Nature Communications* (2023). DOI: 10.1038/s41467-023-35880-y

Provided by Brigham and Women's Hospital

Citation: Genome-wide CRISPR screens identify PARP inhibitor sensitivity and resistance in prostate cancer (2023, April 4) retrieved 17 January 2024 from https://medicalxpress.com/news/2023-04-genome-wide-crispr-screens-parp-inhibitor.html