Introduction

In recent years, PARP inhibitors such as Olaparib, have been established as a proficient strategy to treat homologous recombination (HR) deficient cancers such as ovarian and breast cancer. But it is less efficient to treat homologous recombination efficient and RAS mutant tumors. We attempted to identify candidates whose loss of function can make homologous recombination efficient and make RAS mutant tumors more sensitive to PARP inhibitor treatment. We performed genome-wide CRISPR knockout (KO) screens in ovarian and colorectal cancer cell lines in presence of PARPi (Olaparib). We identified several key components of the DNA damage repair pathway such as BRCA1, BRCA2, RAD50, FANCID2 and FEN1. In addition to these known players in the DNA damage repair pathway, we found UBA1 (a major ubiquitination activation enzyme) as a top depleted gene. We validated the CRISPR screen finding by using siRNAs targeting UBA1 and found that depletion of UBA1, sensitizes ovarian, breast, and colorectal cancer cell lines to PARPi treatment.

Methods

The workflow of this project consisted of conducting genome-wide CRISPR KO screens to identify candidates whose loss can sensitize ovarian and colorectal cancer cell lines to PARPi. We also planned to validate the CRISPR KO screen findings in vitro and in vivo.

Results & Figures

Conclusions

Our CRISPR KO screens identified several key components of the DNA damage repair pathway such as BRCA1, BRCA2, RAD50, FANCID2 and FEN1. In addition to these known players in the DNA damage repair pathway, we found UBA1 (a major ubiquitination activation enzyme) as a top depleted gene in both CRISPR KO screens. Further we validated the CRISPR KO findings and found that depletion of UBA1, sensitizes ovarian, breast, and colorectal cancer cell lines to PARPi treatment. To conclude, our study suggests that the combination of PARPi with UBA1 inhibitor could be a potential therapeutic target for HR efficient and RAS mutant tumours.

Future Research

We planned to mechanistically dissect the synergy between PARP and UBA1 inhibitor.

We planned to further investigate the efficacy of Olaparib treatment with UBA1 inhibitor (FAK243) in vivo by using ovarian, breast, and colorectal xenograft model.

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References