OXPHOS and pharmacological response to PARP inhibition in ovarian cancer

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Background and Aim

Ovarian cancer is the most fatal of all female reproductive cancers. Its treatment was transformed when the first PARP inhibitors (PARP**i**) were approved. PARP are enzymes involved in the DNA repair and their inhibition causes cell damage and death only in cells in which the homologous recombination (HR) pathway is defective.

Recent observations hinted that there might be an interplay between HR status and cellular metabolism. I*n vivo* experiments previously performed in the laboratory suggested that tumors defective in HR might depend on oxidative phosphorylation (OXPHOS).

Our aim is to investigate the reciprocal relationship between OXPHOS and sensitivity to PARP inhibition.

Model of study and experimental procedure

Cell lines

HR proficient

Murine ID8 *Trp53*$^{-/-}$
Human SK-OV-3
Human CAOV-3

HR deficient

Murine ID8 *Trp53*$^{-/-}$ *Brca2*$^{-/-}$
Human OVCAR-3

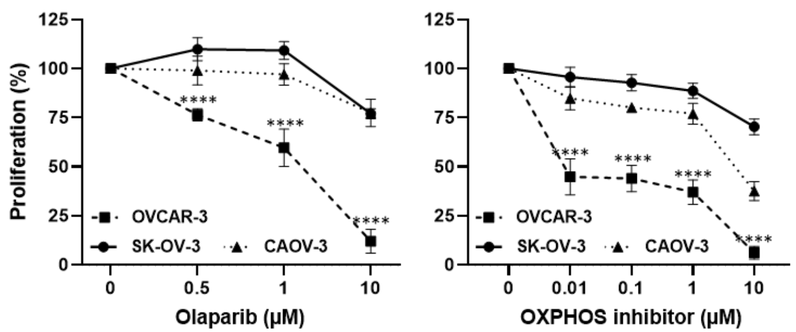
Sensitivity to PARP inhibition was evaluated using Olaparib; modulation of metabolism was obtained using an OXPHOS inhibitor (OXPHOS**i**).

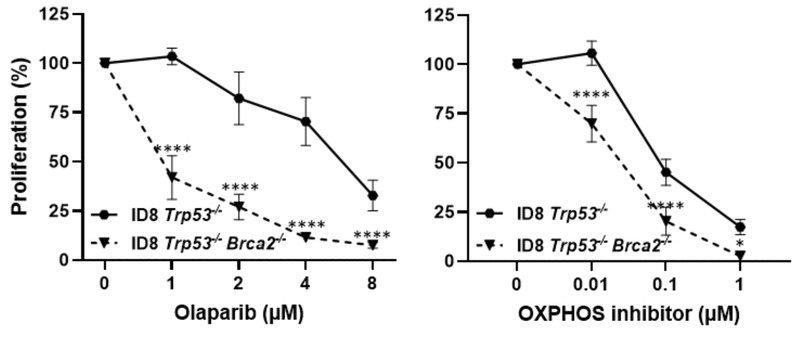
Proliferation assay: 5000 cells/well were seeded in a 96-well plate and treated with indicated drugs after 48h. Cell proliferation was measured after 96h by crystal violet staining.

Colony formation assay: 1000 cells/well were seeded in a 6-well plate and treated with indicated drugs after 72h. Colonies were stained with crystal violet after 120h and counted with Colony Plus software.

Results

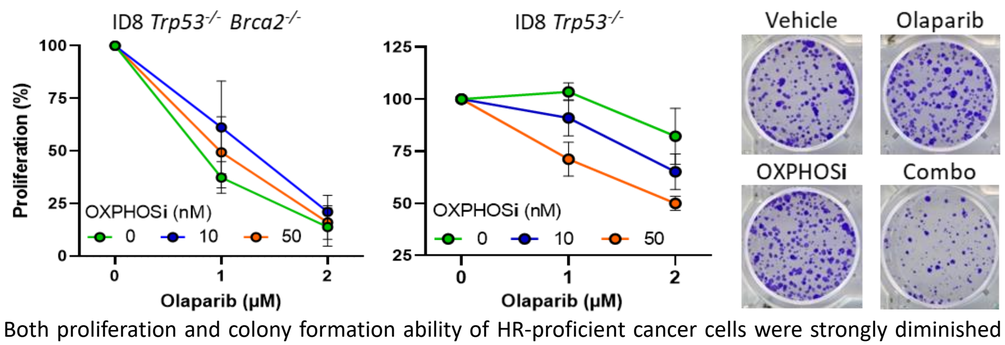
HR-proficient and -deficient cancer cells show different sensitivity not only to PARPi, but also to OXPHOS inhibition





Proliferation of HR-deficient cancer cells was significantly impaired upon Olaparib treatment, as expected, but also after OXPHOS inhibition. HR-proficient cancer cells proliferation was negligibly altered by both treatments.

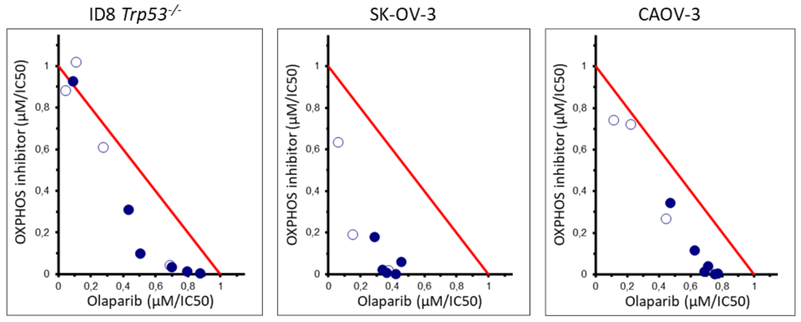
HR-proficient cancer cells were affected by simultaneous inhibition of OXPHOS and PARP pathways



Both proliferation and colony formation ability of HR-proficient cancer cells were strongly diminished after combination treatment.

The inhibition of both pathways is synergistic

Isobologram analysis of the antiproliferative activity of the combination.



Combined concentrations producing IC50 were calculated by fitting dose–response curves of OXPHOS**i** at each tested Olaparib concentration and vice versa. Points below the red line indicate that the effect of the combination at the IC50 level is synergistic.

Conclusions

1. HR-proficient cancer cell lines are poorly affected by PARP inhibition and OXPHOS alteration.
2. OXPHOS**i** and Olaparib combination significantly reduced HR-proficient cancer cells proliferation.

These results confirm an interplay between metabolism and sensitivity to PARP inhibition and suggest that OXPHOS perturbation could sensitize HR-proficient cancer cells to PARP**i**.

Future perspectives

Studies are ongoing to investigate the molecular mechanism linking PARP inhibition, the HR pathway and OXPHOS and the synergistic effect of the OXPHOS**i** and Olaparib *in vivo*.