Defining the effects of PARP inhibition on androgen receptor function in homologous recombination- proficient prostate cancer

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Background: Recent clinical trials have explored the combination of androgen receptor (AR) pathway inhibitors and poly (ADP-ribose) polymerase (PARP) inhibitors as a potential treatment for advanced prostate cancer. Despite promising preclinical evidence, this combination therapy has shown limited efficacy in patients with homologous recombination (HR)-proficient tumors. To investigate this discrepancy between preclinical and clinical results, we profiled the effects of PARP inhibition on AR function in HR-proficient models.

Methods: We used RNA-sequencing to profile the effects of PARP inhibition on AR function in HR-proficient prostate cancer cells using the PARP1/2 inhibitors olaparib and rucaparib and the PARP1-selective inhibitor AZD-5305. We measured DNA repair and the growth effects of PARP inhibitor treatment under androgen deprivation or treatment with the AR antagonist enzalutamide. To distinguish between AR-specific and cell-cycle related effects we used CDK4/6 inhibitors to halt cell cycle progression.

Results: RNA-sequencing analysis demonstrates that PARP inhibition modulates AR transcriptional activity in both castration-sensitive and castration-resistant disease. However, contrary to prior reports, we find no evidence that AR regulates the DNA damage response at the transcriptional level. In concordance with this, we find that PARP inhibition does not synergize with AR pathway inhibition despite the PARP-inhibitor mediated effects on AR-driven transcription. Instead, we find that cell cycle progression is required for response to PARP inhibitors in HR-proficient prostate cancer. Indirect cell cycle inhibition through AR-mediated effects (androgen deprivation, enzalutamide treatment) and direct cell cycle inhibition (through CDK4/6 inhibition and serum starvation) dramatically impaired response to PARP inhibitors. Conversely, restoring cell cycle progression in androgen-deprived cells through androgen treatment re-sensitized cells to PARP inhibitor treatment.

Conclusions: Collectively, our results indicate that while PARP inhibitors mediate AR transcriptional function, they do not synergize with androgen deprivation or AR inhibition in HR-proficient prostate cancer cells. Instead, we demonstrate that therapeutic response to PARP inhibition requires cell cycle progression in HR-proficient prostate cancer, suggesting caution in combining PARP inhibitors with cell-cycle altering drugs.

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