Mapping Mitochondrial Interactions with Endoplasmic Reticulum and Plasma Membrane Under DNA Damage in Prostate Cancer Cells

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Introduction. Prostate Cancer is the second leading cause of cancer death in men in US. The primary treatment for prostate cancer is androgen deprivation therapy (ADT). If cancer progresses while being treated with ADT, the cancer is classified as metastatic castration-resistant prostate cancer. Poly (ADP-ribose) polymerase inhibitors (PARPi) have demonstrated promising results for castration-resistant (and castration-sensitive) prostate cancer. However, some patients develop resistance to PARPi. The mechanisms of action of these drugs are not fully understood and are vital to overcoming PARPi resistance. Therefore, the aim of this study is to fill our knowledge gap of how PARPi affects organelle crosstalk, specifically mitochondrial interactions with the endoplasmic reticulum and plasma membrane.

Methods. LNCaP and MDA PCa 2b, androgen-sensitive cell lines, were treated with 12.5 μM of Olaparib and Rucaparib (FDA-approved PARPi) for 48 hours. A proximity ligation assay (PLA) was used to highlight mitochondrial interactions with the endoplasmic reticulum and with the plasma membrane. Confocal microscopy was used to image these interactions. Kamoshita's (2023) protocol was modified and implemented to quantify the number of interactions between the organelles in the PLA. A pretrained machine learning model, Cellpose, was used to segment the nuclei and obtain an average number of interactions between organelles per cell.

Results. When treated with Olaparib and with Rucaparib, LNCaP cell lines had more mitochondria-endoplasmic reticulum interactions compared to the control ($P<0.05$). There were no significant changes in the number of mitochondria-plasma membrane interactions in LNCaP cell lines when treated with PARPi. There were no significant changes in the number of mitochondria-endoplasmic reticulum and mitochondria-plasma membrane interactions in MDA PCa 2b cell lines when treated with PARPi.

Conclusion. Findings suggest that PARPi affects organelle crosstalk in prostate cancer cells. Further research should investigate how PARPi affects organelle crosstalk in PARPi-resistant cancer cells to improve patient outcomes.