

## **Androgen Receptor Variants Mediate DNA Repair Following Radiation in Prostate Cancer**

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Recently, the combination of androgen deprivation therapy (ADT) and radiation therapy (RT) has been shown to block the androgen receptor (AR)-driven DNA damage response (DDR) and enhance RT-mediated cell kill of prostate cancer (PCa). Since ADT may induce expression of AR splice variants (ARVs) we hypothesized that ARVs can drive DDR and mediate resistance to combined ADT and RT. Herein, we demonstrate that ARVs can increase the clonogenic survival of PCa cells following RT in an ADT-independent manner. RT induces the interaction between ARVs and a DDR driver, the DNA-dependent protein kinase catalytic subunit (DNA-PKc). Pharmacological inhibition of DNA-PKc blocks its interaction with ARVs and results in persistence of DNA damage, increased tumor cell kill and improved PCa cell survival following RT. These results indicate that combinatorial targeting of DNA-PKc with ADT and RT may be an effective strategy for overcoming radioresistance when treating clinically localized PCa.

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