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PROSTATE CANCER

Potential of PARP inhibition plus ADT in prostate cancer

The use of poly(ADP-ribose) polymerase (PARP) inhibitors in combination with androgen deprivation therapy (ADT) shows potential for the treatment of high-risk prostate cancer, according to a new study published in *Nature Communications*.

"Radiation therapy kills tumour cells by inducing DNA double-strand breaks (DSBs)," says Mohammad Asim, a corresponding author on the new paper. "Repair of such radiation-therapy-induced DSBs occurs via a DNA DSB repair pathway called homologous recombination. As radiation therapy synergizes with ADT, we hypothesized that androgen receptor (AR) signalling is associated with radiation-therapy-induced DNA DSB repair and, therefore, we wanted to study the role of AR signalling in DNA repair by homologous recombination. We knew that inhibition of the homologous recombination pathway could trigger PARP activation, and we knew that if AR signalling regulates homologous recombination, we would see PARP activation by ADT."

The authors hypothesized that blocking AR signalling by ADT could trigger back-up survival pathways, thereby causing ADT failure. Using prostate cancer cell lines and a prospective clinical study, they demonstrated that PARP-mediated repair pathways are indeed upregulated in prostate cancer tissue after ADT. As homologous recombination inhibition activates PARP, they also tested whether the AR regulates homologous recombination pathways. They used cell growth assays, tumour xenografts and fresh human tissue *ex vivo* models to test the effect of inhibiting the AR and PARP on tumour growth.

"This study revealed that the AR regulates the homologous recombination and, therefore, that AR inhibition by ADT can trigger the PARP prosurvival pathway," says Asim. "We uncovered the molecular basis of combining ADT with DNA damage (such as radiation therapy or PARP inhibition) and showed that ADT alone can allow prostate cancer to upregulate PARP prosurvival pathways to resist cell death. Although no previous studies linking AR with DNA damage were available when we started this work in 2011, since then a few studies have been published showing that the AR regulates the DNA damage repair by upregulating nonhomologous end joining — another DNA DSB repair pathway — indicating a wider role of the AR in regulating DNA DSB repair."

"ADT alone can lead to accumulation of homologous recombination defects," says Asim. "Although ADT works initially, this approach could allow increased mutational burden and might, therefore, lead to ADT-resistant castration-resistant prostate cancer. Thus, to harness the maximum benefit, the study findings recommend combining ADT with a PARP inhibitor upfront for the treatment of hormone-naive locally advanced disease to inhibit PARP activation and cell survival, an inadvertent effect of ADT."

Rebecca Kelsey

> "...the study findings recommend combining ADT with a PARP inhibitor..."

ORIGINAL ARTICLE Asim, M. *et al.* Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. *Nat. Commun.* **8**, 374 (2017)