The TMPRSS2-ERG fusion gene radiosensitizes to PARP inhibition by blocking DNA repair

Radiotherapy, which is used widely in the clinic, produces DNA damage that leads to DNA double-strand breaks (DSBs). The effectiveness of radiotherapy is augmented when the DNA repair is impaired. TMPRSS2-ERG is a unique fusion gene that is prevalent in prostate cancer patients. We discovered that it blocks non-homologous end-joining (NHEJ) DNA repair, a major mechanism for repair of radiotherapy-induced DSBs. It does so by inhibiting the activity of a critical kinase, DNA-PKcs, and thus destabilized critical NHEJ components on chromatin. Thus, we found that another critical NHEJ component, XRCC4, was not recruited to chromatin, with retention of the other NHEJ core factors being reduced. TMPRSS2-ERG, by inhibiting NHEJ DNA repair, enhanced Poly(ADP-ribose) Polymerase (PARP) inhibitor-mediated radiosensitization. Radiotherapy in combination with PARP inhibition by rucaparib resulted in enhanced DNA damage in TMPRSS2-ERG-expressing tumor cells, leading to enhanced toxicity. Thus, by inhibiting NHEJ, TMPRSS2-ERG provides a synthetic lethal interaction with PARP inhibition in prostate cancer patients, most of which express TMPRSS2-ERG.

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Publication

The TMPRSS2-ERG Gene Fusion Blocks XRCC4-Mediated Nonhomologous End-Joining Repair and Radiosensitizes Prostate Cancer Cells to PARP Inhibition.
Chatterjee P, Choudhary GS, Alswillah T, Xiong X, Heston WD, Magi-Galluzzi C, Zhang J, Klein EA, Almasan A
Mol Cancer Ther. 2015 Aug