Linking EMT to DNA damage response and PARPi resistance in prostate cancer

Reem Malek[1], Rajendra P. Gajula[1], Russell D. Williams[1], Belinda Nghiem[2], Brian W. Simons[3], Hailun Wang[1], Mustafa Barhuiya[1], Theodore L. DeWeese[1,3,4], Paula J. Hurley[3,4], Colm Morrissey[2], Kenneth J. Pienta[3,4]and Phuoc T. Tran[1,3,4]

1. Department of Radiation Oncology and Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA
2. Department of Urology, University of Washington, Seattle, WA, USA
3. Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA
4. Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background:
Sensitivity of metastatic prostate cancers to PARP inhibition in patients that have defects in Homologous Recombination (HR) has been well established. In absence of mutations in HR genes, other factors may prop up this pathway and targeting these pathways can sensitize cancers to PARP inhibitors (PARPi). In leukemia driven by MLL-fusion proteins, HOXA9 can lead to increased expression of HR genes thereby facilitating resistance to PARPi therapy. Inhibiting HOXA9 resulted in restoring sensitivity of MLL positive AML cells to PARPi.

TWIST1 is a master transcriptional regulator of the EMT that plays key roles during development and can promote cancer metastasis. We have demonstrated that TWIST1 activates transcription of HOXA9 which contributes to the induction of a TWIST1-dependent metastatic phenotype in prostate cancer. Further, we have found that TWIST1 forms a complex with the MLL/COMPASS methyltransferase complex and this complex activates HOXA9 expression by H3K4me3 chromatin modification of the HOXA9 promoter region.

The goal of this project is to determine whether HOXA9 expression downstream of TWIST1 can increase DNA repair efficiency in prostate cancer, thereby contributing to PARPi resistance.

Methods and Results: Using *in-vitro* assays for survival, proliferation, homologous recombination, we found that TWIST1 overexpression in cells with low TWIST1 increases the survival of PCa cells in presence of PARPi. Increased *TWIST1* expression corelated with increased DNA repair efficiency and expression of DDR genes, including those important for homologous recombination pathway. In reciprocal experiments, we found that genetically or pharmacologically targeting TWIST1 in cells with high TWIST1, reduced expression of DDR genes and increased sensitivity of these cells to PARPi. Future studies will confirm these findings *in*-vivo using xenograft assays. We will further elucidate the mechanisms by which TWIST1 modulates DDR pathways. Additionally, we aim to identify biomarkers that corelate with TWIST1 overexpression in PCa patients to demarcate patients that would benefit from this combination.

Conclusions:
Overall our results suggest that the EMT transcription factor, TWIST1, can modulate DDR pathways either directly or indirectly which can lead to PARPi resistance. Additionally, targeting TWIST1 and its downstream effectors may be a viable strategy to sensitize recalcitrant PCas to PARPi therapy. Currently, PCas with mutations in DDR genes (~30%) show high response rates with PARPi therapy. From this study, we will able to determine whether a novel subset of aggressive PCa can be made susceptible to PARP inhibitor therapy.

Conflict of Interest: The authors declare that there is no conflict of interest.

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