TWIST1-mediated regulation of HOXA9 promotes resistance to PARPi in Prostate Cancer

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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 HR efficiency in prostate cancer, thereby contributing to PARPi resistance.

Results:
We found that TWIST1 is expressed along with HOXA9 in the developing prostate with peak expression occurring at ~ E17.5. TWIST1 and HOXA9 are re-expressed in mouse prostate cancer. Importantly, we found co-expression of TWIST1 and HOXA9 in a subset of primary CaP tumors in patient samples and their expression was significantly enriched in metastatic samples. Furthermore, alterations in TWIST1 and HOXA9 were associated with decreased survival in patient data from cBIO. In support of our previous data, we show that inhibition of HOXA9 using a peptide inhibitor decreased the pro-metastatic behavior of TWIST1 overexpressing Myc-CaP and PC3 cells in vitro and in vivo.

Conclusions:
TWIST1 plays key roles during development and is a master transcriptional regulator of epithelial plasticity programs that can promote cancer metastasis. We demonstrate that HOXA9 may be a target of TWIST1 during development and this phenomenon is reactivated in CaP progression. In addition to promoting metastasis, HOXA9 expression may lead to PARPi resistance. HOXA9 inhibition shows anti-metastatic behavior suggesting that HOXA9 is a potential target for combination therapy in metastatic CaP.

Conflict of Interest:
Author declared no conflict of interest

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