Sensitization to PARP Inhibition by Co-Targeting TWIST1-HOXA9 in Prostate Cancer

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Background:

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. We have found that TWIST1 forms a complex with the MLL2/COMPASS methyltransferase complex and this complex activates *HOXA9* expression by H3K4me3 chromatin modification of the *HOXA9* promoter region.

Personalized molecular strategies to identify which prostate cancer patients are more likely to respond to specific treatment would result in better outcomes and less overtreatment with minimally effective agents. A recent example is the sensitivity of metastatic prostate cancers to PARP inhibition in only those patients that have defects in DNA damage response (DDR). Recently, acute myelogenous leukemias positive for Mixed Lineage Leukemia (MLL) fusion proteins have been shown to overexpress HOXA9 which in turn leads to increased expression of DDR genes thereby facilitating resistance to PARP inhibitor therapy. Inhibiting HOXA9 resulted in restoring sensitivity of MLL positive AML cells to PARP inhibitors.

The goal of this project is 1) to investigate whether HOXA9 expression occurs along with TWIST1 *in vivo* and 2) determine whether HOXA9 can lead to expression of DDR genes in prostate cancer which would lead to PARP inhibitor resistance and 3) determine whether inhibiting HOXA9 will dampen TWIST mediated pro-metastatic responses and sensitize these cells to PARP inhibition.

Materials/Methods:

We used *in vitro* assays that mimic the various stages of cancer progression to metastasis. The MSKCC cBioPortal was used to perform CaP expression analysis. *In vivo* lung colonization assays were performed using peptide inhibitors of HOXA9. IHC on autochthonous mouse prostate tumors and patient samples were performed.

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 at least one model of 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 the EMT that promotes cancer metastasis. We demonstrate that HOXA9 may be a target of TWIST1 during development and this phenomenon is reactivated in CaP progression. We show that HOXA9 inhibition can dampen TWIST dependent pro-metastatic behavior suggesting that HOXA9 is a potential target for combination therapy in metastatic CaP.

Conflict of Interest Statement:
In relation to this presentation, the authors declare that there are no conflicts of interest.

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