MEIS proteins inhibit HOXB13-dependent prostate cancer metastasis and Androgen Receptor signaling

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Background: Prostate cancer (PCa) is one of the most frequently diagnosed malignancies in men, and its incidence and mortality continue to be a significant clinical problem. Recent evidence from our lab identified MEIS1, an important HOX protein cofactor, as a potential tumor suppressor. Patients bearing MEIS1-positive prostate tumors were less likely to have biochemical recurrence and metastasis compared to men bearing MEIS-negative tumors. Androgen receptor (AR), the major oncogene in PCa, has been shown to interact with HOXB13 to promote prostate cancer progression, but the function of MEIS proteins to antagonize AR/HOXB13 interactions are unknown. We hypothesize that MEIS1 proteins interact with HOXB13 to suppress cancer initiation and progression, and loss of MEIS1 expression in a portion of prostate tumors enables oncogenic AR/HOXB13 interactions.

Methods: We determined the impact of MEIS1 expression and dependency of HOXB13 on AR signaling using cell lines ectopically expressing MEIS1 and/or CRISPR-mediated HOXB13 deletion in both androgen-sensitive LAPC4 and castration-resistant CWR22Rv1 cells. Western blots, qPCR, Proximity Ligation Assay and co-IPs were performed to evaluate the relationship among MEIS1, HOXB13 and AR. Hormonally-intact and castrated male nude mice were used to test the *in vivo* capability of MEIS1-mediated tumor formation and rate of tumor growth in the presence and absence of AR ligand.

Results: We found that AR expression was significantly increased when MEIS1 was ectopically expressed compared to controls and HOXB13 knock-out lines. Re-expression of MEIS1 enhanced the binding between HOXB13-MEIS and AR-MEIS, and reduced the AR-HOXB13 interaction. In castrated mice, re-expression of MEIS1 significantly decreased the tumor formation and tumor growth rate compared to hormonally intact nude mice. Conversely, xenografts of HOXB13-knockout tumors showed an increased rate of tumor growth and tumor formation compared to MEIS1-expressing cells and controls in both hormonally intact and castrated nude mice.

Conclusion: Our collective data supports our hypothesis that increased MEIS1 expression reduces the AR/HOXB13 interaction and increases the *in vivo* sensitivity to host castration; this suggests that MEIS-positive cells have decreased oncogenic AR signaling. Future RNAseq studies will determine the global impact of MEIS expression on AR gene targeting in PCa and provide us a strong rationale to support the potential utility of MEIS proteins as predictive clinical biomarkers of metastatic progression.

Funding: This work was supported by the Urology Care Foundation Research Scholar Award, DOD grant PC130587, and DOD grant PC180414.

Conflict of Interest Disclosure statement: No disclosures and no conflicts of interest