GSTP1 regulates the growth and metastasis of castrate resistant prostate cancer

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Introduction & Objective
Prostate cancer is the second leading cause of cancer related deaths among men in the United States. Although, hormone deprivation therapies are initially effective for prostate cancer patients, the disease commonly recurs and advances into a castration resistant state (CRPC). Neuroendocrine prostate cancer (NEPC) is a highly aggressive variant of prostate cancer that usually emerges post treatment resistance. Since there are no curative treatments for CRPC or NEPC, elucidating new therapeutic strategies for advanced disease is urgently needed. GSTP1 promoter hypermethylation is one of the earliest genetic alterations found in localized prostate cancer. Surprisingly, we identified that GSTP1 protein is significantly elevated in a recently developed NEPC model and further demonstrated that GSTP1 can affect advanced prostate cancer growth and metastasis.

Methods
Protein levels of GSTP1 in benign prostate, CRPC, and NEPC patient-derived xenografts (PDXs) were analyzed by immunohistochemistry. Knockdown of GSTP1 was achieved by short hairpin RNAs in a TROP2-driven NEPC cell line model and in DU145 and PC3 cell lines. The effect of GSTP1 knockdown was assessed by colony formation, cell proliferation, and matrigel drop invasion assays *in vitro*. The role of GSTP1 expression on prostate cancer growth and metastatic colonization was evaluated *in vivo* by subcutaneous xenograft implantation and intracardiac injection.

Results
GSTP1 protein expression was elevated in CRPC and NEPC cell lines and PDXs. Knockdown of GSTP1 expression decreased prostate cancer tumor growth and invasion *in vitro* and metastatic colonization *in vivo*. Furthermore, GSTP1 inhibition by Piperlongumine (PPLGM) suppressed prostate cancer cell growth, migration, and invasion.

Conclusions

GSTP1 is a novel druggable target for CRPC and NEPC. GSTP1 knockdown by shRNA or a small molecule inhibitor, PPLGM, decreases tumor growth and migration in prostate cancer.