Androgen receptor acetylation modulates proliferation of castrate-resistant prostate cancer

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Background
Androgen receptor (AR) lysine residues 630/632/633 are acetylated in response to androgen-binding. An AR mutation that mimics this modification occurs in a subset of prostate cancer patients (K630T), and increased levels of AR acetyltransferases have been observed in some advanced cases. We hypothesize that acetylation contributes to aberrant AR activation in castrate-resistant prostate cancer, contributing to tumor growth and viability.

Methods
Genetic and pharmacologic approaches are being utilized to determine the function of AR acetylation in castrate-resistant disease, both in cell culture and in *in vivo* models. C4-2 cell lines have been generated within which endogenous AR (shRNA) is stably knocked down and acetylation-mutant AR (acetylation-null, acetylation-mimic, or lysine-intact controls) is expressed. The effect of AR acetylation on castrate-resistant cell growth in culture and tumor growth *in vivo* has been evaluated. Microarray analysis of cultured cells has been performed to investigate transcriptomic changes that occur when AR acetylation is blocked. Migration assays have been performed based on microarray results. Antibodies against acetylated AR have been created and are being characterized in prostate cancer cell lines.

Results
Acetylation-null AR expressing C4-2 cells had a substantially reduced growth rate in culture and in xenograft tumors. Mice injected with these cells had a substantially reduced tumor take. Acetylation-mimic AR-expressing cells have a growth advantage over controls in culture, and, in castrated mice, these xenograft tumors grew faster than controls. Microarray revealed gene expression changes in a number of cellular pathways in acetylation-null AR-expressing cells. A member of MMP family was substantially downregulated. As such, we found that acetylation-null expressing C4-2 cells migrate less than controls, and acetylation-mimic expressing C4-2 cells have increased migration over controls. Moreover, pharmacologic activation of an AR deacetylase and pharmacologic inhibition of an AR acetyltransferase reduced growth and induced death of C4-2 cells.

Conclusions
Our data indicate that AR acetylation plays a critical role in castrate-resistant disease and that it may also contribute to a metastatic phenotype. Targeting the enzymes responsible for AR acetylation may be a viable means to treat castrate-resistant disease. Antibodies specific for acetylated AR may enable the evaluation of this AR modification across various disease states.

Conflicts of interest: None to report

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