

AR acetylation modulates growth and viability of castrate-resistant prostate tumors

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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

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 and invasion assays have been performed based on microarray results. Antibodies against acetylated AR have been created and are being utilized to identify the acetylation status of AR in various prostate cancer cell lines following various treatments.

Results

Acetylation-null AR expressing C4-2 cells grow substantially slower in culture, as do xenograft tumors, and tumor take is reduced. Acetylation-mimic AR-expressing cells have a growth advantage over controls in culture, and in castrated mice these xenograft tumors grow faster than controls. Microarray revealed gene expression changes in a number of cellular pathways in acetylation-null AR-expressing cells. An MMP was substantially downregulated and *in vitro* assays revealed that the acetylation-null expressing C4-2 cells migrate less and that acetylation-mimic expressing C4-2 cells are more invasive. Moreover, pharmacologic activation of an AR deacetylase and pharmacologic inhibition of an AR acetyltransferase reduces growth and induces death of C4-2 cells. C4-2 cells also have increased acetylated AR over LNCap cells.

Conclusions

Our data indicate that AR acetylation may play 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. Acetylated AR-specific antibodies may enable the evaluation of this AR modification across various disease states and following various treatment regimens to determine whether this modification is a viable target to treat specific subsets of tumor cells.

Conflicts of interest: None to report

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