Investigating the role of androgen receptor acetylation in castrate-resistant prostate cancer

Erin Heine[4], Matthew Schiewer[2], Victoria Nolte[4], Diane E. Merry[1], Scott Dehm[3], Karen E. Knudsen[2] and **Heather L. Montie[4*]**

Department of Biochemistry and Molecular Biology[1], Departments of Cancer Biology, Urology and Radiation Oncology[2], Thomas Jefferson University and Kimmel Cancer Center, Philadelphia, PA; Department of Laboratory Medicine and Pathology, Masonic Cancer Center, University of Minnesota, Minneapolis, MN[3,] Department of Bio-Medical Sciences, Philadelphia College of Osteopathic Medicine, Philadelphia, PA[4]

[*] presenter

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). Increased levels of AR acetyltransferases have also 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. The goal of our studies is to understand the role of AR acetylation in castrate-resistant prostate cancer.

Methods

We are utilizing genetic and pharmacologic approaches to determine the function of AR acetylation in castrate-resistant disease, both in cell culture and in *in vivo* models. We have generated C4-2 cell lines within which we have stably knocked down endogenous AR (shRNA) and expressed acetylation-mutant AR (acetylation-null, acetylation-mimic, or lysine-intact controls). We have evaluated the effect of AR acetylation on castrate-resistant cell growth in culture and tumor growth *in vivo*. Microarray analysis of cultured cells has been performed to investigate transcriptomic changes that occur when AR acetylation is blocked.

Results

AR acetylation modulated growth of castrate-resistant prostate cancer cells in culture and *in vivo*. Acetylation-null AR expressing C4-2 cells had a substantially reduced growth rate in culture, and this growth pattern was replicated in xenograft tumors. Moreover, 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 analysis revealed gene expression changes in a number of cellular pathways in acetylation-null AR-expressing C4-2 cells. Both 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. They also suggest that targeting the enzymes responsible for AR acetylation is a viable means to treat castrate-resistant disease. Further studies targeting these enzymes *in vivo* are warranted. Whether AR acetylation is a driver of castrate-resistant disease is still an open question that we are working to answer.

Conflicts of interest:

None to report

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