Targeted suppression of AR-V7 using PIP5K1α inhibitor overcomes enzalutamide resistance in prostate cancer cells

Martuza Sarwar1, Julius Semenas2, Regina Miftakhova3, Athanasios Simoulis4, Brian Robinson5, Anette Gjörloff Wingren6, Nigel P. Morgan2, David M. Heeys, Heather Johnson9, Per-Anders Abrahamsson10, Nishtman Dizeyi10, Jun Luo11, Azharuddin Sajid Syed Khaja2, Jenny L. Persson1,2

Introduction: Prostate cancer (PCa) is the most common malignancy, and the third leading cancer-related cause of death among men in western world. One mechanism of resistance to enzalutamide (MDV3100) treatment is the increased expression of AR variants lacking the ligand binding-domain, the best characterized of which is AR-V7. We have previously reported that Phosphatidylinositol-4-phosphate 5-kinase alpha (PIP5Kα), is a lipid kinase that links to CDK1 and AR pathways.

Methods: Immunohistochemistry, with tumors from patients with PCa. Xenografts mouse models bearing Enzalutamide resistant 22Rv1 cells. Cell proliferation, immunofluorescence, immunoprecipitation, flow cytometry and western blot analyses were performed.

Results:
- AR-V7 expression positively correlates with PIP5K1α in tumor specimens from PCa patients.
- Overexpression of AR-V7 increases PIP5K1α, promotes rapid growth of PCa in xenograft mice, whereas inhibition of PIP5K1α by its inhibitor ISA-2011B suppresses the growth and invasiveness of xenograft tumors overexpressing AR-V7.
- We have identified PIP5K1α and CDK1 as important co-factors for both AR-V7 and AR, which are present as protein-protein complexes predominantly in the nucleus of PCa cells.
- In addition, PIP5K1α and CDK1 influence AR-V7 expression also through AKT-associated mechanism dependent on PTEN-status.
- Inhibition of PIP5K1α by ISA-2011B leads to a reduction in the expression of AR-V7 and invasive activity of xenograft tumors.
- We show that ISA-2011B selectively inhibits both AR-V7 and AR, thus overcomes treatment resistance to enzalutamide.

Conclusion: Our study suggests that combination of enzalutamide and PIP5K1α may have a significant impact on refining therapeutic strategies to circumvent resistance to antiandrogen therapies.

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