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

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Abstract

One mechanism of resistance of prostate cancer (PCa) 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---phosphate 5-kinase alpha (PIP5Ka), is a lipid kinase that links to CDK1 and AR pathways. The discovery of PIP5Ka inhibitor highlight the potential of PIP5K1α as a drug target in PCa. In this study, we show that 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. PIP5K1α is a key co-factor 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. ISA-2011B disrupts protein stabilization of AR-V7 which is dependent on PIP5K1α, leading to suppression of invasive growth of AR-V7-high tumors in xenograft mice. 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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Keywords

AR-V7, Enzalutamide resistance, Lipid kinase inhibitor, PIP5K1α, Prostate cancer metastasis