

Targeting of the PI3K/AKT pathway overcomes enzalutamide resistance by inhibiting the induction of glucocorticoid receptor

Remi M. Adelaiye-Ogala¹, Berkley Gryder², Yen Thi Minh Nguyen¹, Aian Neil Alilin¹, Adlai Grayson¹, Keith H. Jansson¹, Michael L. Beshiri¹, Supreet Agarwal¹, Jose Antonio Rodriguez-Nieves¹, Brian Capaldo¹, Kathleen Kelly¹ and David J. VanderWeele^{1,3}

¹Laboratory for Genitourinary Cancer Pathogenesis, Center for Cancer Research, National Cancer Institute, NIH Bethesda, MD, ²Oncogenomics Section, Genetics Branch, National Cancer Institute, NIH Bethesda, MD, ³Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: An evolving concept that contributes to the understanding of resistance to androgen deprivation therapy and/or androgen receptor (AR) antagonist in prostate cancer (PCa) is the ability of the cells to bypass AR blockade and turn on compensatory hormone signaling for survival. Recent preclinical and clinical studies demonstrate that induction of GR expression confers resistance to AR-targeted therapy. Hence therapeutic strategies to overcome GR mediated resistance are warranted. **Experimental Design:** Models of PCa were exposed to the pan-AKT inhibitor ipatasertib or other PI3K/AKT- pathway inhibitors with/without AR blockade. Gene array determined differentially expressed AR/GR target genes. H3K27ac deposits for active enhancers and protein expression levels were assessed. Cell viability and tumor growth was determined in response to treatment. **Results:** AKT inhibitor as monotherapy significantly decreases cell viability across multiple prostate cancer models. The cytotoxic effect is enhanced by AR inhibition and is most pronounced in models that induce compensatory GR expression. Ipatasertib as well as other inhibitors of the PI3K/AKT pathway decreased GR activity through AR-dependent mechanisms. Importantly, AKT inhibition, with/without AR blockade, demonstrated significant anti-tumor activity in several in vivo prostate cancer models with no noticeable toxicity. **Conclusion:** Inhibition of the PI3K/AKT pathway blocks GR activity and overcomes GR-mediated resistance to AR-targeted therapy. This therapeutic approach has immediate clinical relevance as ipatasertib is currently in advanced clinical development and provides a supportive tool for how to manage patients with acquired resistant to AR-targeted therapy.

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