Androgen receptor drives polyamine synthesis creating a vulnerability for prostate cancer

Rajendra Kumar, Sheila Jonnatan, David E Sanin, Varsha Vakkala, Anoushka Kadam, Shivani Kumar, Susan L Dalrymple, Liang Zhao, Jackson Foley, Cassandra E Holbert, Ashley Nwafor, Elizabeth Penner, Petya Apostolova, Samuel Warner, Victoria Sinibaldi, Keith McIntyre, Eugene Shenderov, Catherine H Marshall, Kenneth J Pienta, Michael A Carducci, Adel Mandl, Channing J Paller, Mark C Markowski, Kathy Schultz, Annette Timlin, Hao Wang, Elizabeth A Thompson, Chi V Dang, Angelo M De Marzo, John T Isaacs, Erika L Pearce, Tracy Murray Stewart, Robert A Casero Jr, Samuel R Denmeade, Laura A Sena

Affiliations: Johns Hopkins University; Baltimore, MD, USA

Background: The androgen receptor (AR) is a nuclear hormone receptor with context-dependent function. We and others have shown that it can paradoxically suppress cancer progression in castration-resistant prostate cancer (PCa) treated with supraphysiological androgens (SPA), a therapy known as bipolar androgen therapy (BAT). BAT results in objective responses for about 30% of patients with metastatic castration-resistant PCa and portends a median progression-free survival of 6 months. We previously demonstrated that response to BAT is associated with a marked decrease in tumor expression of the oncogene MYC. Given that AR and MYC are master regulators of metabolism, we sought to define metabolic consequences and vulnerabilities induced by SPA treatment of PCa models.

Methods: Global metabolomics and metabolite isotope tracing were utilized to assess changes to metabolic flux in PCa models treated with SPA. The mechanism by which SPA regulates polyamine production and the functional consequence was interrogated by genetic and pharmacologic perturbation of the SPA – AR – ornithine decarboxylase (ODC) – S-adenosylmethionine decarboxylase (AMD1) signaling axis. Mechanisms by which SPA and ODC inhibition enhance PCa growth suppression was assessed by RNAseq and modulation of intracellular S-adenosylmethionine pools. Global metabolomics of plasma samples from patients treated with BAT and the ODC inhibitor, difluoromethylornithine (DFMO), assessed metabolic effects of this combination treatment.

Results: SPA can alter PCa metabolism in part by increasing de novo polyamine synthesis. This increase in polyamine synthesis is driven by AR binding upstream of the *ODC1* gene, which encodes ODC, one of the rate-limiting enzymes in this pathway, and is paradoxically augmented by downregulation of MYC, which antagonizes AR induction of *ODC1*. SPA-stimulated polyamine synthesis facilitates resistance to growth inhibition by SPA, as genetic or pharmacologic disruption of this signaling axis enhances growth inhibition by SPA. This occurs in part through activation of AMD1 and depletion of S-adenosylmethionine (SAM) pools leading to enhanced repression of MYC. Initial results from the first 5 patients on a clinical trial of BAT in combination with the ODC inhibitor DFMO indicate that DFMO can effectively inhibit ODC in patients, resulting in accumulation of its precursors arginine and ornithine and reduction of its products putrescine and spermidine in patients with metastatic PCa, even upon treatment with testosterone.

Conclusions: The AR is a key positive regulator of polyamine synthesis across normal and malignant tissues. The induction of polyamine synthesis can facilitate resistance to growth inhibition by SPA in models of PCa. An ongoing clinical trial (NCT06059118) will test whether inhibition of polyamine synthesis will increase response to BAT in patients with metastatic castration-resistant PCa.

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