

Inhibition of fatty acid synthase suppresses the androgen receptor and its splice variant V7 and reduces castration resistant prostate cancer growth.

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Background: Altered lipid metabolism has been recognized as a hallmark of cancer cells and a growing body of literature has shown the relationship between increased *de novo* lipogenesis and prostate cancer (PCa) initiation and progression. Fatty acid synthase (FASN), an androgen-regulated enzyme, is responsible for the *de novo* synthesis of long-chain fatty acids (FAs). Up-regulation of FASN represents a nearly universal phenotypic alteration in PCa. Its enhanced enzymatic activity provides the building blocks for macromolecules as well as fuel for FA oxidation, thus promoting tumorigenesis. Importantly, overexpression of FASN is highest in metastatic castration resistant prostate cancer (mCRPC), suggesting a role for FASN in promoting androgen independence. The androgen receptor (AR) plays critical growth and survival roles in PCa. Although initially sensitive to androgen deprivation therapy, virtually all PCas become resistant to the most current AR inhibition treatments, namely abiraterone and enzalutamide. As AR blockade has improved, diverse resistance mechanisms are increasingly observed, most notably the emergence of ligand-independent AR splice variants (AR-V).

In this study, we evaluated the anti-cancer effect of the pharmacological inhibition of FASN in PCa and its impact on both lipid metabolism and AR signaling.

Methods: We tested the potent and specific orally bioavailable irreversible FASN inhibitor (IPI-9119), provided by Infinity Pharmaceuticals in a large panel of androgen-dependent and CRPC cell lines. Biochemical (FASN activity, *de novo* lipogenesis, FA oxidation) and cell biology (cell proliferation, cycle, and apoptosis) endpoints were used to evaluate the anti-tumor properties of the inhibitor. The Effect of FASN inhibition on AR signaling was evaluated by immunoblotting for AR full length (AR-fl) and AR-V7 in a panel of enzalutamide and abiraterone resistant PCa cell lines. Cell growth and AR/AR-V7 rescue experiments were performed by addition of exogenous palmitate. The anti-tumor effect of IPI-9119 *in vivo* was evaluated in a xenograft model of CRPC (22RV1).

Results: Incubation of IPI-9119 in several androgen-sensitive and CRPC PCa cells resulted in cell growth reduction and cell cycle arrest concomitant with the suppression of both *de novo* lipogenesis and FA beta-oxidation. Addition of exogenous FA palmitate, the product of FASN activity, significantly rescued this phenotype. Importantly, a significant downregulation of AR and its splice variant V7 was observed upon prolonged treatment with IPI-9119 in LNCaP cells, enzalutamide and abiraterone resistant LNCaP-95, 22RV1, and VCaP cells. Again, AR-fl, AR-V7 and the downstream target PSA was rescued by addition of exogenous palmitate. *In vivo*, IPI-9119 reduced tumor growth in 22RV1-xenograft model.

Conclusion: Our results provide evidence for a reciprocal regulation between FASN and AR pathway and suggest that inhibition of FASN may represent a potential therapeutic strategy for CRPC in the setting of resistance to enzalutamide and abiraterone. Moreover, the dissection of the biochemical and molecular mechanisms whereby inhibition of *de novo* lipogenesis affects AR and AR splice variant expression and signaling will define a new approach to the treatment of CRPC.

Conflict of Interest Statement: Nothing to declare.

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