GENETIC AND PHARMACOLOGICAL INHIBITION OF FATTY ACID SYNTHASE ATTENUATES PROSTATE CARCINOGENESIS DRIVEN BY PTEN LOSS.

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INTRODUCTION AND OBJECTIVES: PTEN loss in murine prostates recapitulates human prostate carcinogenesis. Overexpression of fatty acid synthase (FASN), essential enzyme for the endogenous lipogenesis, is associated with worse prognosis for prostate cancer (PCa). PTEN and FASN levels are inversely correlated in human PCas. Targeting lipid metabolism may represent an attractive therapeutic strategy in the context of PCa driven by PTEN loss. The goal of this study is to evaluate the effect of the genetic ablation of Fasn in prostate-specific Pten knockout (KO) mice, and analyze the enzymatic inhibition of FASN in PTEN⁻/⁻ PCa cells.

MATERIAL AND METHODS: In vivo: C57/Bl6/SVJ129 Ptenwt/loxP/Fasnwt/loxP/Pb-Cre⁺ male mice and Ptenwt/loxP/Fasnwt/loxP/Pb-Cre⁻ females were crossed to generate prostate-specific Pten and Fasn double KO mice. The size, weight and histopathology of the ventral lobe in the Pten/Fasn KO group were compared with the controls at 12 and 40 weeks. In vitro: Biochemical and cell biology endpoints were used to evaluate the antitumor effect of the irreversible FASN inhibitor IPI-9119 (Infinity Pharmaceuticals) in a panel of PTEN⁻/⁻ human PCa cells.

RESULTS AND DISCUSSION: Genetic ablation of Fasn in Pten KO mice reduced the incidence of high-grade PIN and abrogated the PCa phenotype. Incubation of IPI-9119 in several PTEN⁻/⁻ human PCa cells resulted in cell growth reduction, cell cycle arrest, induction of apoptosis, and suppression of both de novo lipogenesis and fatty acid beta-oxidation. Addition of exogenous fatty acid palmitate, the product of FASN activity, partially rescued this phenotype. Importantly, a significant downregulation of androgen receptor (AR) was observed in LNCaP cells upon prolonged treatment with IPI-9119, suggesting a reciprocal regulation between FASN and AR pathway.

CONCLUSION: De novo lipogenesis contributes to the tumorigenic phenotype induced by PTEN loss in the prostate. These results provide a rationale for exploring the concomitant use of inhibitors of FASN and of the PTEN signaling pathway in PCa.