

Breaking the fat chain: FASN inhibition and exogenous PUFAs as a double hit against Prostate Cancer progression.

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Background: Prostate cancer progression is characterized by dysregulated lipid metabolism, with activation of fatty acid synthase (FASN), the rate-limiting step in *de novo* lipogenesis (DNL), resulting in significantly increased synthesis of saturated lipids. Here, we show that pharmacologic FASN inhibition creates a metabolic state that increases reliance on exogenous polyunsaturated fatty acids (PUFAs).

Methods: Hormone-sensitive (LNCaP) and castration-resistant (C4-2, 22Rv1) prostate cancer cells were treated with the FASN inhibitor IPI-9119 (100 nM), DHA (100 μ M), or both for 6 days. Lipid remodeling, oxidative stress, mitochondrial function, and cell death were assessed by lipidomics and biochemical assays. Hi-Myc mice received fatty-acid-defined diets with or without FASN inhibition, followed by histopathologic and lipidomic analyses.

Results: Pharmacologic inhibition of FASN profoundly alters membrane phospholipid composition, driving compensatory incorporation of PUFAs into membrane phospholipids, this remodeling increases the availability of oxidation-prone phospholipid substrates, and it is followed by increased ACSL4, reduced GPX4, lipid peroxidation, and oxidative damage. Combined FASN inhibition and exogenous PUFA exposure suppress prostate cancer cell growth, induce mitochondrial hyperpolarization, and enhance lipid peroxidation in both hormone-sensitive and castration-resistant prostate cancer models, resulting in increased reactive oxygen species production and activation of both ferroptotic and apoptotic cell-death programs.

In vivo, genetically engineered Hi-Myc mice treated with FASN inhibitor, and a diet enriched in PUFAs, but not a saturated fat-enriched diet, significantly inhibited invasive carcinoma. Thus, PUFA availability is a determinant of response to FASN-targeted strategies, with PUFA supplementation enhancing the vulnerability created by DNL blockade. Circulating and tumor lipidomic signatures of dietary exposure and FASN target engagement provide a biomarker framework for integrating precision nutrition with pharmacologic intervention in prostate cancer.

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