Global changes in membrane lipid metabolism by inhibition of fatty acid synthase in prostate cancer

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Background: A hallmark of prostate cancer progression is dysregulation of lipid metabolism via overexpression of fatty acid synthase (FASN), a key enzyme in de novo fatty acid synthesis. Castration resistant prostate cancer (CRPC) develops resistance to inhibitors of androgen receptor (AR) signaling through a variety of mechanisms, including the emergence of constitutively active AR variants. Previously, we studied an irreversible FASN inhibitor (IPI-9119) and demonstrated that IPI-9119 promoted endoplasmic reticulum (ER) stress, which inhibited protein expression and transcriptional activity of both full-length AR and AR variants. Because ER stress is known to be influenced by membrane lipids, the goal of this study was to investigate the lipid metabolic effects of IPI-9119 in prostate cancer.

Methods: AR-positive LNCaP and AR/AR-variant positive LNCaP95 cells were treated with IPI-9119 over a 6-day time course. Cell pellets were subjected to comprehensive lipidomic profiling of over 1800 lipid species across 16 different lipid classes. We performed integrative analysis of lipidomic changes and gene expression changes observed in RNA-seq data from IPI-9119 treated cells.

Results: IPI-9119 induced a progressive decrease in the levels of abundant triacylglyceride (TAG) species in both cell lines. Interestingly, treatment with IPI-9119 promoted a progressive increase in specific membrane sphingolipid species, which matched the kinetics of reduced AR and AR variant protein expression in these cell line models. An increase in sphingolipid levels in response to IPI-9119 treatment was consistent with concomitant up-regulation in gene expression levels of *CERS2* and *CERS4*, which encode sphingolipid synthesis enzymes ceramide synthase 2 and 4. IPI-9119 treatment also increased the levels of specific glycerophospholipid (GPL) species, which was accompanied by altered expression of GPL regulators *ACSL1*, *AGPAT2*, and *AGPAT6*.

Conclusions: Inhibition of FASN with IPI-9119 promotes widespread changes in lipid metabolites and expression of genes that regulated lipid metabolism. Our work demonstrates up-regulation of sphingolipids and GPL species with kinetics that mirror the reduction in expression of AR and AR variants in IPI-9119-treated prostate cancer cell line models. We have further identified key regulators of these lipid species that display altered gene expression in response to IPI-9119.