

# Regulation of Prostate Cancer Metabolism and Invasiveness by the Liver X Receptor

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## Background

Growth and metastasis of prostate cancer (PCa) is dependent on several metabolic pathways. During malignant transformation, cancer cells switch to a predominantly glycolytic metabolism. This aerobic glycolysis, also called “the Warburg effect”, provides essential substrates for tumor cell growth. Tumors also exhibit enhanced lipogenesis. These glycolytic and lipogenic pathways are specifically vital to castrate resistant tumors. The liver-X-receptor (LXR) is a transcriptional regulator expressed in prostate epithelial cells that plays a key role in cholesterol, lipogenic, and carbohydrate homeostasis. High LXR expression is linked to increased PCa recurrence and metastasis. We hypothesize that it is possible to disrupt LXR mediated metabolic pathways with use of LXR ligands, thus providing a possible treatment for PCa.

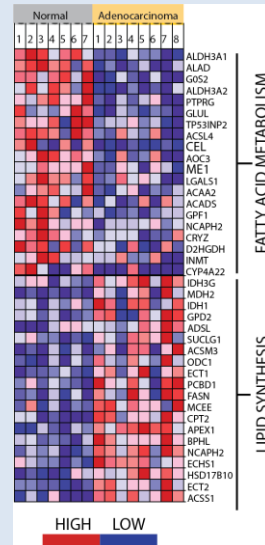
## Methods

- RNA from patient derived prostate samples were sequenced to determine if prostate tumors are dependent on lipid synthesis enzyme expression (lipogenesis)
- LXR and lipogenesis gene expression was quantified using qPCR in androgen sensitive and insensitive cultured PCa cells to determine if LXR expression correlates with lipogenesis activation
- The effect of LXR inhibition using the inverse agonist SR9243 on androgen sensitive and insensitive PCa cells was compared
- The ability of SR9243, to inhibit AR-Insensitive tumor growth was tested *in vitro* and in *in vivo* rodent PCa models

## Results

**Figure 1. Prostate Tumors are reliant on Lipid Synthesis**

- Tumors show low expression of fatty acid metabolism enzymes
- Tumors have high expression of lipid synthesis (lipogenesis) enzymes
- The Liver-X-Receptor LXR regulates a number of lipid synthesis enzymes identified in tumors (e.g. FASN)

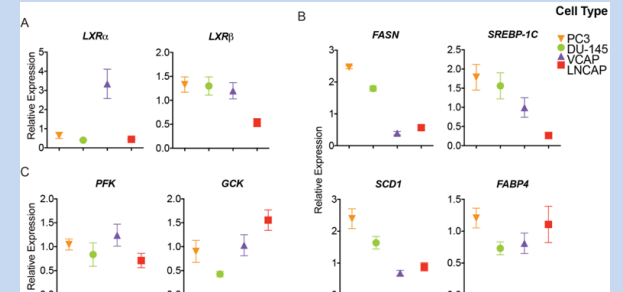


## Conclusions

- LXR regulates metabolic pathways that are vital to prostate cancer growth and metastasis
- High LXR expression is correlated with prostate cancer metastasis and androgen insensitivity
- Inverse agonists of the LXR receptor may be a feasible treatment for prostate cancer

**Figure 2. LXR target gene expression correlates with lipogenesis gene expression and AR-sensitivity in prostate cancer cells.**

- LXR expression was highest in AR-Insensitive cancer cells



**Figure 3. The LXR Inverse Agonist SR9243 Selectively Kills Metastatic AR-Insensitive Prostate Cancer Cells**

- Suppressed lipogenesis gene expression
- Inhibited AR-Insensitive/null prostate cancer cell growth
- Reduced tumor volume
- Blocked tumor lipid production
- Induced tumor cell death through apoptosis

