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CPT1A Expression Modulates Growth, Endocrine Resistance and Histone Acetylation in Prostate Cancer

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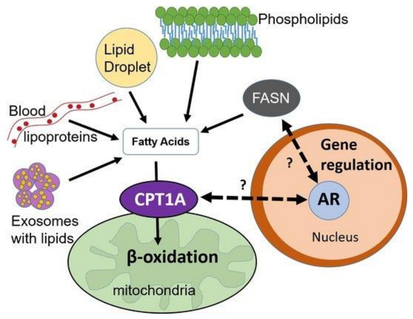
Background

Prostate cancer is the most diagnosed and the second most common cause of cancer-related death among men in the United States. Targeting metabolic changes in cancer cells may enable the development of novel therapies or the enhancement of existing treatments. Understanding the role of patient metabolism in prostate cancer may lead to lifestyle or diet changes that can improve treatment success. Hormone-dependent cancers of the prostate preferentially use fatty acid oxidation (FAO) as their primary source of energy. Carnitine palmitoyltransferase 1A (CPT1A), an enzyme that is overexpressed by these cancers, shuttles long-chain fatty acid into the mitochondria and controls the rate-limiting step of FAO. Inhibiting CPT1A is known to delay tumor growth, but the role of CPT1A in aggressive prostate cancer is still poorly understood.

Figure 1. CPT1 is the rate-limiting enzyme for beta oxidation of long-chain fatty acids. FFA come from various sources including internal stores, exosomes and blood lipoproteins. The androgen receptor (**AR**) modulates lipid metabolism but its mechanisms in cancer are still unknown.



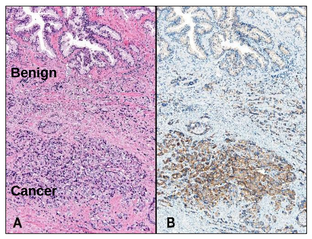
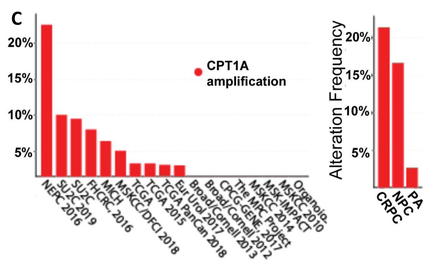


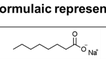
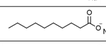
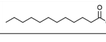
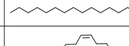
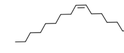
Figure 2. CPT1A expression in prostate cancer. (**A-B**) Representative images of serial sections of benign and cancer tissue obtained from the same radical prostatectomy specimen, stained with (A) hematoxylin and eosin or (B) CPT1A-specific stain. **(C)** cBioportal data of recent studies in prostate cancer showing CPT1A amplification frequency. **PA**= adenocarcinoma, **NPC** = neuroendocrine, **CRPC**= castration resistant.



Materials & Methods

We investigated how CPT1A expression impacts factors important in the study of prostate cancer: lipid metabolism and androgen receptor (AR) signaling.
We based our experiments on genetic models of castration-resistant prostate cancer (CRPC). C4-2 and 22RV1 cell lines were each modified to create four genetic models: CPT1A knockdown (**KD**), CPT1A overexpression (**OE**), and their controls. Clonogenic assays were used to evaluate growth potential for each CPT1A cell line with fatty acid (FFA) treatments. Seahorse flux analysis was used to assess lipid oxidation. Five FFA (octanoic, decanoic, dodecanoic, palmitic, and oleic) were conjugated to BSA and used to treat the cells at the indicated doses, **Table 1.** Histone acetylation marks in the presence (FBS) and absence (CSS) of androgens were assessed by western blot.
Castrated mice were used to implant C4-2 and 22Rv1 cells and study their growth in response to CPT1A expression and the anti-androgen enzalutamide (20 mg/Kg/day).

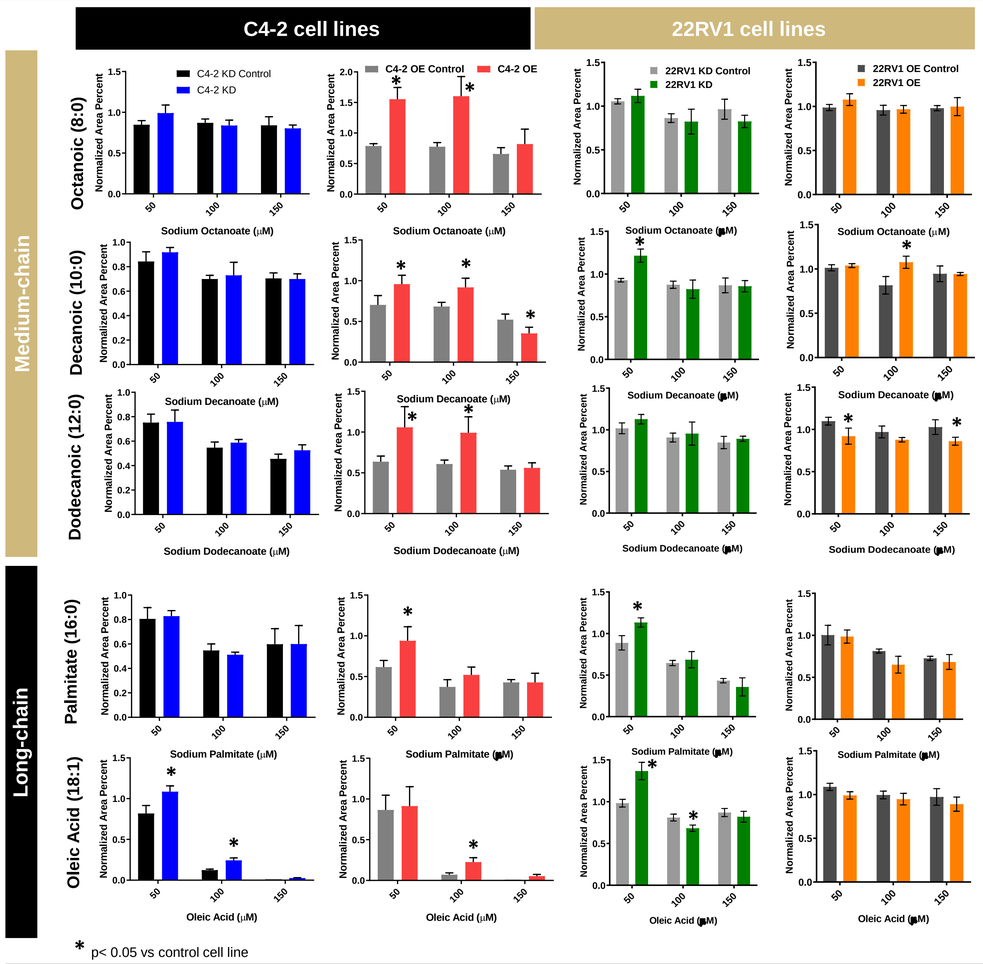
Table 1. Fatty acid treatments and their common sources

Fatty acid name and classification	Formulaic representation	Common everyday sources
Sodium octanoate (medium-chain FA)		Milk; some found in coconut oil and palm kernel oil
Sodium decanoate (medium-chain FA)		Coconut oil; some found in milk and palm kernel oil
Sodium dodecanoate (medium-chain FA)		Coconut milk, coconut oil, laurel oil, palm kernel oil; some found in milk
Sodium palmitate (long-chain FA)		Palm oil, sunflower oil, coconut butter, soybean oil, dairy, meat
Oleic acid (long-chain FA)		Olive oil, avocados

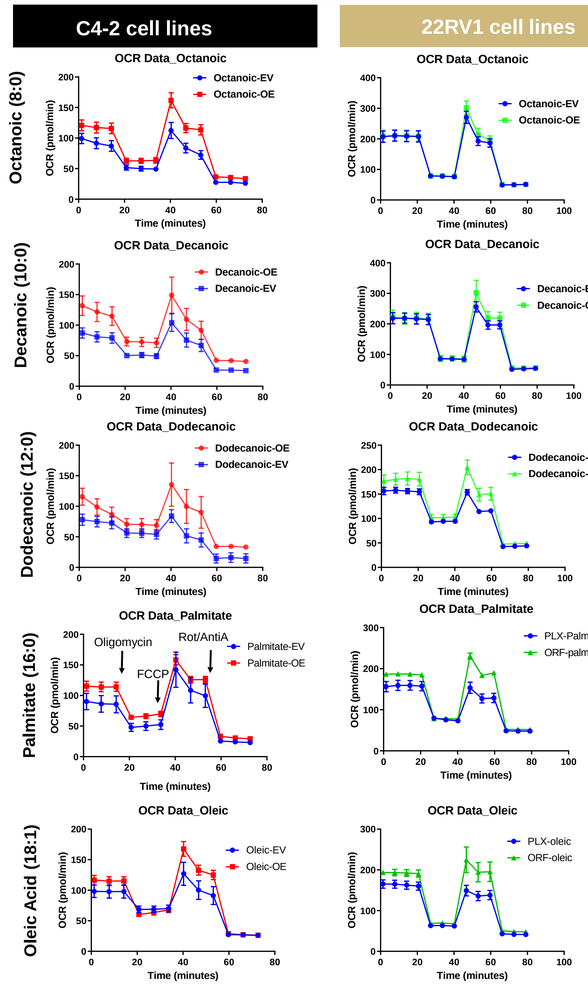
Acknowledgements

Funding support from American Cancer Society RSG 16-256-01-TBE, Cancer League of Colorado AWD-163158-IS and UROP Mini Grant, 2018-2019.
Special thanks to Maren Salzmann, Juliana Oviedo and Lauren Liebman for their insight and technical support.

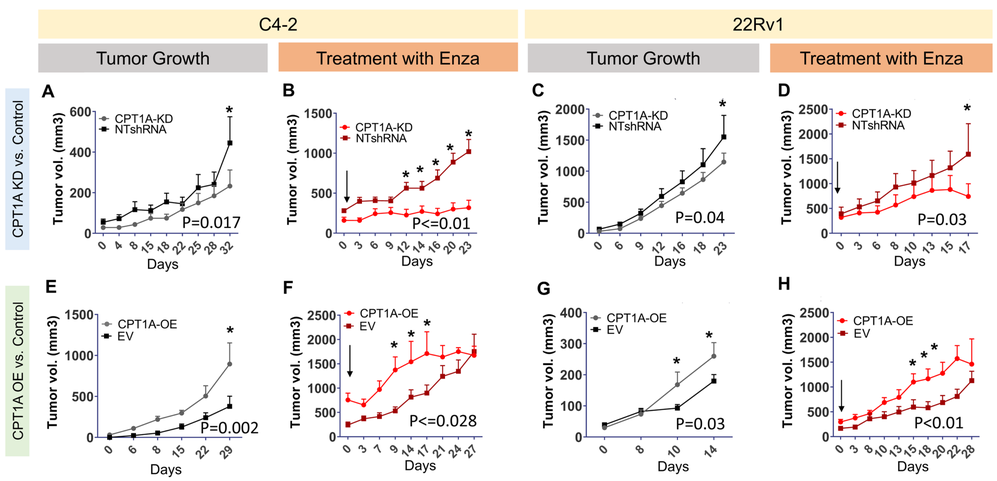
Results



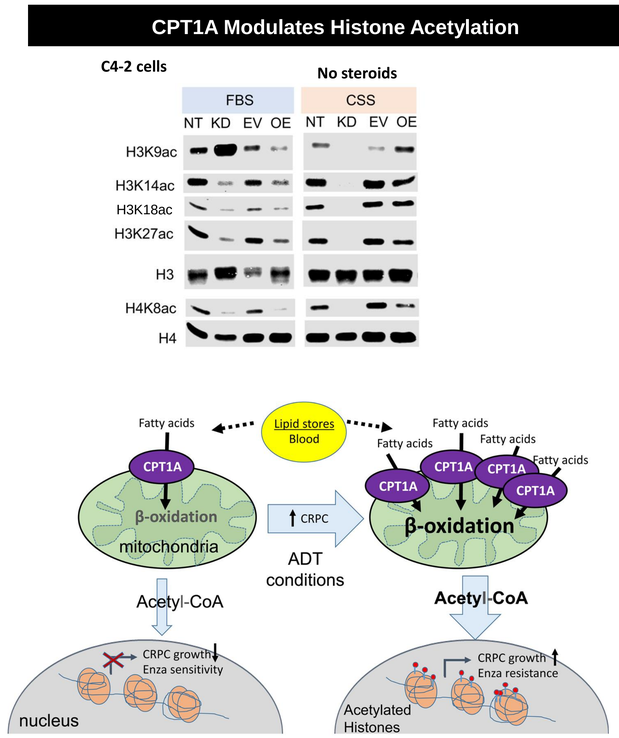
* p< 0.05 vs control cell line



Enzalutamide Effects on Growth are Associated with CPT1A Expression



CPT1A Modulates Histone Acetylation



Conclusions & Future Directions

- Increased CPT1A expression results in more lipid burning capacity and growth when cells are supplemented with fatty acids, including medium chain fatty acids, which was unexpected. This has implications for popular MCT oil diets and the risk of hormonal cancers.
- CPT1A x enzalutamide interaction *in vivo* suggests an inverse relationship between CPT1A and androgen signaling. This may explain high CPT1A amplification in neuroendocrine and CRPC, Figure 2c.
- CPT1A activity provides acetyl groups for histone acetylation in androgen-deprived conditions, linking lipid metabolism and epigenetic regulation in CRPC.
- Future studies with different fatty acid-based diets will inform about the role of dietary lipid composition on prostate cancer therapy response and outcomes.