Role of UDP-Glucose Dehydrogenase (UGDH) in Prostate Tumor Cell Response

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Introduction

- Prostate cancer is the second leading cause of cancer death in United States men (American Cancer Society, 2015).
- Cancer initially occurs in an androgen-dependent state where the cancer cells rely primarily on the male hormones interacting with the androgen receptors (AR) for growth and survival.
- Cancer cells that initially respond to treatment tend to develop into an androgen-independent state commonly referred to as castration-resistant prostate cancer (CRPC).
- Growth of CRPC has been associated with increased expression of AR.
- UDP-glucuronosyltransferase (UGT) enzymes have begun to receive increased attention due to their capacity to effectively reduce lipophilic hormone and xenobiotic concentrations by glucuronidation.
- Through glucuronidation, chemical substrates are inactivated while also solubilizing them for urinary excretion.

Methods and Materials

- Cell count was conducted and cells set in standard conditions (24 hrs).
- After 48hrs, media was replaced with 10% CS-10%FBS and left to “starve” (48 hrs).
- Dilutions at the various concentrations of DHT from stock solution were prepared.
- Media was replaced with fresh 10%CS-10%FBS, and left to “starve” (48 hrs).
- After 48hrs, a complete lysate extraction was performed.
- Western Analysis conducted probing for αUGDH and αPSA.

Results

- Figure 1 above shows after 96-hours of androgen deprivation the UGDH (shown in green) expression had decreased in comparison to those with the various concentrations of DHT.
- Figure 2 above shows after 96-hours of androgen deprivation the expression had decreased in comparison to those with the various concentrations of DHT.

Discussion

- Androgen-independent growth in prostate cancer is a poorly understood phenomena and is the source of recurrent aggressive cancer.
- High levels of hyaluronan (HA) turnover in prostate cancer have been correlated with aggressive cancer progression, but while UGDH expression is high within the cell, HA is virtually undetectable.
- Thus, UGDH’s natural function may be to provide the necessary precursors for UGT enzymes that are involved in the glucuronidation pathway.
- In our study, we quantified the androgen-dependence of UGDH in the androgen-dependent cell line VCaP.
- We were able to show that the vCaP cells respond to DHT with a bell-shaped UGDH-expression curve.

Potential Role of UGDH:

- Testosterone (T) is synthesized at the tissue level, or delivered in circulation, and converted into dihydrotestosterone (DHT).
- T and DHT are substrates of UGT2B15/17, which use the UGDH product UDP-glucuronate (UDP-GlcA) as a cofactor for glucuronidation.
- UGDH is DHT-stimulated in the ligand-dependent AR pathway and drives glucuronidation, which is thought to be a negative feedback regulator to rid the cell of excess androgens.
- With the affinity of UGTs for androgen being lower than that of the AR, significant elevation of UGDH-GlcA is needed to drop cellular androgens below the level of cellular response.
- This elevation, found in luminal cells of cancerous acini, could promote ligand-independent function of the AR.

VCAP Cells

- UDP-Glucose Dehydrogenase Gene
- GPRO Cells
- AR
- T
- DHT
- UDP-Glucose
- Glucuronidation
- Excretion

Future Work

- Continued exploration into UGDH’s role within VCaP cell line
- Growth Assays on UGDH altered cell lines
- Treatment of UGDH-altered cell lines with Abiraterone, a medicine commonly used in the treatment of metastatic prostate cancer.

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