Targeting DHEA-S Transport and Steroid Sulfatase for More Efficient Androgen Deprivation Therapy

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Abstract MP29-11

Background

- Testosterone (T) and dihydrotestosterone (DHT) activate androgen receptor (AR), which is important to prostate cancer.
- Prostate cancer cells are capable of intratumoral (intracrine) production of T and DHT.
- Adrenal androgens are the most abundant androgens in humans. Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) are the major adrenal androgens in circulation.
- DHEA-S and DHEA may serve as substrates for intracrine T/DHT production.
- Concentrations of DHEA-S and DHEA in circulation are ~3.5 to 10 μM and ~ 10 nM, respectively.
- Steroid sulfatase (STS) hydrolyzes DHEA-S to DHEA.
- DHEA-S and DHEA may serve as substrates for intracrine T/DHT production.
- DHEA contributes to 50% prostate DHT in Intact men (Labrie et al., 2005).

The present study addressed the capability of prostate cancer cells to use DHEA-S and DHEA for T/DHT production, delineate signaling pathways activated by DHEA-S and DHEA, and determine whether adrenal androgens sustained tumor growth after ADT.

Experimental Procedures

- Expression of STS was examined using qRT-PCR and immunohistochemistry (IHC).
- Metabolism of DHEA-S and DHEA in intact tissue specimens was evaluated ex vivo using fresh clinical prostate tissue.
- Tissue specimens were cut into 1.3-mm pieces. Pieces of tissue were cultured in phenol red-free RPMI 1640 supplemented with 10% charcoal-stripped fetal bovine serum (CS-FBS).
- DHT or DHEA in culture medium was measured using ELISA.
- Growth of subcutaneous VCaP xenograft in vivo
- Severe combined immunodeficiency (SCID) or nude mice were “humanized” to mimic human circulating T levels
  - Surgical removal of testes
  - T-silastic tubing implant to “humanize”
  - T-silastic tubing removal to castrate
- DHEA treatment with DHEA-silastic tubing
- IGF1R inhibitor BMS-754807 was delivered via oral gavage.

Results

- Fig 1. STS expression in matched benign and malignant prostate tissue specimens at (A) mRNA levels (n=20) and (B) at protein levels, and (C) in human prostate cancer cell lines at mRNA levels.
- Prostate tissue used DHEA-S and DHEA to produce DHT ex vivo
- DHT production by prostate tissue ex vivo was STS-dependent. STX64, an STS inhibitor. A much higher DHT production on day 4 than day 1 was noted. Low levels of DHT production in control. Lower concentrations of DHEA-S and DHEA, and STX64 conditions were noted, although the data points were shown to be close to 0 in the graphs due to the large scale in the Y-axis.
- Prostate cancer cell lines used DHEA-S and DHEA to produce DHT
- DHEA-S activated AR in prostate cancer cell lines
- DHEA-S and DHEA stimulated growth of human prostate cancer cells
- Adrenal androgens may have AR-independent functions in prostate cancer cells
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- DHEA stimulated growth of VCaP xenograft after castration in SCID mice (A-C) and nude mice (D-F).
- Tabled showed ratios of growth rates between treatment groups that were compared.

Conclusions

- Prostate tissue uses adrenal androgens for DHT production.
- DHEA-S is the most available adrenal androgen for DHT production.
- Adrenal androgens stimulate AR activity and support cell growth.
- Cancer promoting activities of adrenal androgens may be mediated by AR-dependent and AR-independent pathways.
- Identification of potential targets, and therapeutics to block adrenal androgen-stimulated pathways, are necessary to treat prostate cancer.

Support for research

This study was supported by NIH grants 1R21CA191895-01 (YW) and 1R01CA193829-01A1 (GS & YW, PIs).

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