A Role for Estrogen Receptor Beta in the Inhibition of Prostate Cancer Cell Growth

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Introduction

Prostate cancer and benign prostatic hypertrophy are highly prevalent pathologies in men and are known to be heavily influenced by the degree of androgen exposure.

The presence of both androgen receptors (AR) and estrogen receptor beta (ERβ) have been well-characterized in prostate and prostate tumor cells.

ARs have strong proliferative activity in prostate, however, recent studies have implicated an anti-proliferative role for ERβ.

Several compounds have been identified to bind to ERβ, namely the synthetic ERβ agonist diarylpropionitrile (DPN), the dihydrotestosterone (DHT) metabolite 5 alpha androstane-3 beta 17b diol (3b diol), and the isoflavone metabolite, equol (a daidzein-derived compound with phytoestrogen properties).

By studying the effects of these ERβ agonists on normal prostate growth in a mouse model and on human Prostate cancer cell growth in vitro, we attempted to elucidate the interplay between concurrent androgen and ERβ stimulation on prostate growth and prostate cancer cell proliferation.

Methods

In Vitro Model: LnCaP cells were grown to 80% confluency and were then treated with either 5nM DHT, 10nM 3beta diol, 10 nM S-DPN, 20 uM Equol, or Vehicle (ethanol <0.1% in RPMI 1640 media containing charcoal-stripped 10% fetal bovine serum) for 2 days. Live cells and dead cells were weighed.

In Vivo Model: Adult male rats (ages 90-100 days) were injected for 10 days with equol (n=5, 10mg/kg) in NaCl) for 21 days. Prostate lobes were individually dissected and weighed.

Sprague-Dawley rats from Charles River age 90-100 days old were injected for 10 days with equol (n=3) while fed phyto-free diet. Cells: A comparison Study Using DNA Microarray.

Results

3b diol did not significantly influence LnCaP cell proliferation.

DPN decreases dorsolateral lobe weight in mice.

Summary and Discussion

Summary:

As expected, DHT increased prostate cell proliferation as indicated by a relative decrease in dead cell population compared to control, suggesting an anti-apoptotic effect.

Furthermore, equol demonstrated anti-proliferative effect in cells when alone as well as in the presence of DHT.

Equol also demonstrated a significant decrease in Rat prostate, namely the dorsolateral lobe which is known to be the most homologous to the human peripheral zone, the site of most carcinomas.

DPN treatment of LNcaP cells decreased cell proliferation, an effect that interestingly was overcome by concurrent treatment with DHT. DPN also decreased dorsolateral prostate lobe weight in mice.

ββββ did not significantly alter cell growth, but does show an interesting trend of blocking the anti-apoptotic effect of DHT.

Conclusions:

These data suggest an anti-proliferative role of some ERβ agonists, notably DPN and equol.

Furthermore, in vitro and in vivo data strongly suggest an antagonistic action of Equol on effects of DHT not seen by DPN.

The cellular signaling pathway of ERβ stimulation is not yet clear, but this data suggest that different agonists of the same receptor likely trigger different pathways.

The anti-androgen effects of Equol are of paramount importance in regulating/counteracting hormone-induced Prostate cancer cell proliferation and may have future clinical implication in this widely-prevalent disease condition.

Future Direction

What are gene expression profiles in prostate cancer cells following ERβ stimulation +/- DHT?

Does ERβ stimulation interfere with androgen receptor mediated PSA secretion from human prostate cancer cells?

Does ERβ stimulation prevent the development of spontaneous prostate tumors in the TRAMP model of prostate cancer?

Reference


