Journal of Andrology, Vol. 26, No. 4, July/August 2005

DOI: 10.2164/jandrol.05002

Receptor Isoform and Ligand-Specific Modulation of Dihydrotestosterone-Induced Prostate Specific Antigen Gene Expression and Prostate Tumor Cell Growth by Estrogens

YUAN-SHAN ZHU, LI-QUN CAI, YING HUANG, JASON FISH, LU WANG, ZHI-KAI ZHANG AND JULIANNE L. IMPERATO-MCGINLEY

From the Department of Medicine/Endocrinology, Weill Medical College of Cornell University, New York, New York.

Correspondence to: Dr Yuan-Shan Zhu, Department of Medicine/Endocrinology, Weill Medical College of Cornell University, 1300 York Ave, Box 149, New York, NY 10021 (e-mail: yuz2002{at}med.cornell.edu).

Androgens via the androgen receptor (AR) play crucial roles in prostate physiology and pathophysiology. These androgen actions can be either inhibited or potentiated by estrogens. The mechanisms of these seemingly opposing estrogen effects are unclear. We studied the effects of estrogens on the modulation of androgen induction of prostate specific antigen (PSA) gene expression and prostate tumor cell growth. Cotransfection analyses in CV-1, DU-145, and PC-3 cells showed that dihydrotestosterone (DHT)-induced PSA transcription activity was inhibited by 17ß-estradiol, diethylstilbestrol, ICI182780, and 17α-estradiol, but not by tamoxifen via estrogen receptor α (ERα). In the presence of ERß, 17ß-estradiol and diethylstilbestrol had no significant effect, while 17α-estradiol inhibited and ICI182780 and tamoxifen potentiated DHT action. When both ERα and ERß were present, all ER-ligands except tamoxifen inhibited DHT action. The inhibition of DHT action by 17ß-estradiol via ERα was mainly dependent on the DNA binding domain, while the 17α-estradiol effect was mainly dependent on the ERα carboxyl terminus. Treatment with DHT in LAPC-4 prostate tumor cells that express a wild-type AR and both ERß and ERα greatly increased the PSA gene expression and cell growth. These DHT effects were significantly attenuated by the addition of 17α-estradiol, 17ß-estradiol, or cyproterone acetate in a dose-dependent manner. These results indicate that estrogens produce an ER-isoform– and ER-ligand–specific modulation of DHT induction of PSA gene expression and prostate tumor cell growth, providing a molecular basis for designing favorable agents for the prevention and control of prostate cancer.

Key words: Androgen receptor, androgens, estrogen receptor

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM HOME

A. Beleza-Meireles, I. Kockum, F. Lundberg, C. Soderhall, and A. Nordenskjold
Risk Factors for Hypospadias in the Estrogen Receptor 2 Gene
J. Clin. Endocrinol. Metab., September 1, 2007; 92(9): 3712 - 3718.
[Abstract] [Full Text] [PDF]

Molecular Cancer Therapeutics HOME

R. S. Bhattacharyya, A. V. Krishnan, S. Swami, and D. Feldman
Fulvestrant (ICI 182,780) down-regulates androgen receptor expression and diminishes androgenic responses in LNCaP human prostate cancer cells.
Mol. Cancer Ther., June 1, 2006; 5(6): 1539 - 1549.
[Abstract] [Full Text] [PDF]

Journal of ANDROLOGY HOME

S. M. Dehm and D. J. Tindall
Editorial Commentary on Zhu et al
J Androl, July 1, 2005; 26(4): 509 - 510.
[Full Text] [PDF]