The Evolving Role of Oestrogens and Their Receptors in the Development and Progression of Prostate Cancer

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CONTEXT: Oestrogens were proven effective in the hormonal treatment of advanced prostate cancer (PCa) >60 yr ago and are still used as second-line hormonal therapy. Paradoxically, oestrogens might also be involved in the development and progression of PCa. OBJECTIVE: To examine mechanisms of how oestrogens may affect prostate carcinogenesis and tumour progression. EVIDENCE ACQUISITION: Recent data obtained from animal, experimental, and clinical studies were reviewed. EVIDENCE SYNTHESIS: The human prostate is equipped with a dual system of oestrogen receptors (oestrogen receptor alpha [ERalpha], oestrogen receptor beta [ERbeta]) that undergoes profound remodelling during PCa development and tumour progression. In high-grade prostatic intraepithelial neoplasia (HGPIN), the ERalpha is upregulated and most likely mediates carcinogenic effects of oestradiol as demonstrated in animal models. Preliminary clinical studies with the ERalpha antagonist toremifene have identified the ERalpha as a promising target for PCa prevention. The partial loss of the ERbeta in HGPIN indicates that the ERbeta acts as a tumour suppressor. The ERbeta is generally retained in hormone-naïve PCa but is partially lost in castration-resistant disease. The progressive emergence of the ERalpha and the oestrogen-regulated progesterone receptor (PR) during PCa progression and hormone-refractory disease suggests that these tumours can use oestrogens and progestins for their growth. The TMPRSS2-ERG gene fusion recently reported as a potentially aggressive molecular subtype of PCa is regulated by ER-dependent signalling. TMPRSS2-ERG expression has been found to be increased by ERalpha agonist (oestrogens) and decreased by ERbeta agonists. CONCLUSIONS: Oestrogens and their receptors are implicated in PCa development and tumour progression. There is significant potential for the use of ERalpha antagonists and ERbeta agonists to prevent PCa and delay disease progression. Tumours equipped with the pertinent receptors are potential candidates for this new therapeutic approach.

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Tamoxifen and gonadal steroids inhibit colon cancer growth in association with inhibition of thymidylate synthase, survivin and telomerase expression through estrogen receptor beta mediated system

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Estrogen receptor beta (ERbeta) mediated system was tested in three colon cancer cell lines with different sensitivities. These cell lines express ERbeta and androgen receptor (AR) but not the classic estrogen receptor ERalpha. Combinations of ERbeta ligands such as estradiol (E(2)), 17 epiestriol (17E(3)), quercetin (Q) with tamoxifen (TMX) showed marked growth inhibition. The IC(50) were: 2.0+/-0.3x10(-15), 3.0+/-1.3x10(-10) and 1.2+/-0.5x10(-14) M for DLD-1, DLD-1/5FU and DLD-1/FdUrd, respectively (TMX+E(2) treatment, mean+/-SD, n=3). The IC(50) of TMX+17E(3) were 3.5+/-1.8x10(-8), 2.6+/-0.9x10(-8) and 1.4+/-1.1x10(-14) M and that of TMX+Q treatment were 3.4+/-2.1x10(-9), 3.6+/-0.2x10(-9) and 2.6+/-1.1x10(-9) M, respectively. This inhibition was significantly different from single agent treatment at the probability level of P<0.002. Thymidylate synthase expression and survivin expression were also markedly inhibited. The inhibition was highest with TMX+Q and lowest with TMX+dehydroepiandrosterone (DHEA). The expression of telomerase was also inhibited by TMX but combination with ERbeta antagonists reversed the inhibition. The cellular sensitivity to 5FU was increased: TMX+E(2), TMX+17E(3) and TMX+Q were 1.7+/-0.5x10(-5), 8.4+/-3.2x10(-8), 8.2+/-2.9x10(-8) and 6.3+/-3.3x10(-8) M for DLD-1 cells and 7.7+/-4.8x10(-5), 9.1+/-4.9x10(-7), 1.5+/-0.3x10(-9) and 5.7+/-2.2x10(-8) M for DLD-1/FdUrd. DLD-1/FdUrd cells had IC(50) of 8.5+/-6.1x10(-5), 1.8+/-0.8x10(-8), 3.7+/-1.1x10(-9) and 1.6+/-1. x10(-9) M (mean+/-SD) for the control, TMX+E(2), TMX+17E(3) and TMX+Q. The present data indicate that ERbeta ligands in combination with TMX may have tumor static effects on colon cancer cells.

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Evaluation of estrogenicity of major heavy metals
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We have employed an estrogen receptor dependent transcriptional expression assay and E-Screen assay systems to evaluate the estrogenicity of major heavy metals and their species. Using the former, the following estrogenicity ranking was measured: bis(tri-n-butyltin)>cadmium chloride>antimony chloride>barium chloride>chromium chloride>thallium hydroxide>sodium selenate>lead acetate>stannous chloride. Using the latter, the following estrogenicity ranking was measured: bis(tri-n-butyltin)>cadmium chloride>antimony chloride>thallium hydroxide>barium chloride>sodium selenate>chromium chloride. Especially, bis(tri-n-butyltin), cadmium chloride, antimony chloride, thallium hydroxide, barium chloride, and chromium chloride showed estrogenicity in both assay systems. Recent studies suggesting that bis(tri-n-butyltin), cadmium chloride, and thallium hydroxide have estrogenicity are compatible with the present findings. Furthermore, our studies are the first to suggest that antimony, barium, chromium may be estrogenic. A range of estrogenicity was observed for different species of the same heavy metal. The results demonstrate that an estrogen receptor dependent transcriptional expression assay and the E-Screen assay systems could serve as a useful method to assess the estrogenicity of heavy metals.

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