Estrogen Action in Normal Prostate Epithelium and in Prostate Cancer

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1. INTRODUCTION

Estrogens are known to have significant direct and indirect effects on prostate gland development and homeostasis, and have been long suspected in playing a role in the etiology of prostatic diseases. These effects are mediated through estrogen receptors (ERs) ERα and ERβ, which are differentially expressed in prostatic stromal and epithelial cells, respectively, and whose expression changes over time and with disease progression. This chapter will review the evidence for a role of estrogens and specific ERs in prostate growth, differentiation, and carcinogenesis as well as discuss potential therapeutic strategies for growth regulation via these pathways.

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2. ESTROGENS IN THE MALE AND EFFECTS ON THE PROSTATE GLAND

Although low levels of circulating estrogens are present throughout life in males, there are two time periods, in utero development and aging, when males are exposed to relatively higher levels of circulating estradiol which have been shown to impact the prostate gland. In addition, estradiol may be produced locally within the prostate via conversion of testosterone by aromatase expressed within the prostate stroma (1,2). Importantly, prostatic aromatase expression and promoter usage have been shown to shift in prostate cancer, which may contribute significantly to increased intraprostatic estrogen levels during disease progression (3).

During the third trimester of in utero development in humans, rising maternal estradiol levels and declining fetal androgen production result in an increased estrogen/testosterone (E/T) ratio. This relative increase in estradiol has been shown to directly stimulate extensive squamous metaplasia within the developing prostatic epithelium, which regresses rapidly after birth when estrogen levels drop precipitously (4–6). Although the natural role for estrogens during prostatic development is unclear, it has been proposed that excessive estrogenization during prostatic development may contribute to the high incidence of benign prostatic hyperplasia (BPH) and prostatic carcinoma currently observed in the aging male population (7,8). African-American men have a twofold increased risk of prostatic carcinoma as compared with their Caucasian counterparts, and it has been suggested that this is related, in part, to elevated levels of maternal estrogens during early gestation in this population (9,10). Indicators of pregnancy estrogen levels such as length of gestation, pre-eclampsia, and jaundice indicate a significant correlation between elevated estrogen levels and prostate cancer risk (11,12). Furthermore, maternal exposure to diethylstilbestrol (DES), a potent synthetic estrogen agonist, during pregnancy was found to result in more extensive prostatic squamous metaplasia in male offspring than observed with maternal estradiol alone (13). Whereas prostatic metaplasia eventually resolved following DES withdrawal, ectasia and persistent distortion of ductal architecture remained (14). This has lead to the postulation that men exposed prenatally to DES may be at increased risk of prostatic disease later in life, although this has not been borne out in limited population studies conducted to date (15). However, extensive studies with rodent models predict marked abnormalities in the adult prostate, including increased susceptibility to adult-onset carcinogenesis following early estrogenic exposures (7,16–18). Although use of DES during pregnancy was discontinued in the early 1970s, the recent realization that certain environmental chemicals have potent estrogenic activities (19) has lead to a renewed interest in evaluating the effects and roles of exogenous estrogens during prostatic development (20).