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Review

Actions of estrogens and endocrine disrupting chemicals on human prostate stem/progenitor cells and prostate cancer risk

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ABSTRACT

Estrogen reprogramming of the prostate gland as a function of developmental exposures (aka developmental estrogenization) results in permanent alterations in structure and gene expression that lead to an increased incidence of prostatic lesions with aging. Endocrine disrupting chemicals (EDCs) with estrogenic activity have been similarly linked to an increased prostate cancer risk. Since it has been suggested that stem cells and cancer stem cells are potential targets of cancer initiation and disease management, it is highly possible that estrogens and EDCs influence the development and progression of prostate cancer through reprogramming and transforming the prostate stem and early stage progenitor cells. In this article, we review recent literature highlighting the effects of estrogens and EDCs on prostate cancer risk and discuss recent advances in prostate stem/progenitor cell research. Our laboratory has recently developed a novel prostasphere model using normal human prostate stem/progenitor cells and established that these cells express estrogen receptors (ERs) and are direct targets of estrogen action. Further, using a chimeric *in vivo* prostate model derived from these normal human prostate progenitor cells, we demonstrated for the first time that estrogens initiate and promote prostatic carcinogenesis in an androgen-supported environment. We herein discuss these findings and highlight new evidence using our *in vitro* human prostasphere assay for perturbations in human prostate stem cell self-renewal and differentiation by natural steroids as well as EDCs. These findings support the hypothesis that tissue stem cells may be direct EDC targets which may underlie life-long reprogramming as a consequence of developmental and/or transient adult exposures.

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Contents

1. Introduction

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer deaths in North American men (Jemal et al., 2010). It is known that steroids play a role in the initiation and progression of prostate cancer, which is the basis for hormonal treatment strategies that include androgen ablation and androgen receptor (AR) blockade (Eisenberger et al., 1998; Huggins and Hodges, 1941). Increasing evidence indicates that in

Abbreviations: E2, estradiol; EDCs, endocrine disrupting chemicals; AR, androgen receptor; ER, estrogen receptor; PIN, prostate intraepithelial neoplasia; PCBs, Polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; POPs, persistent organic pollutants; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; AhR, aryl hydrocarbon receptor; PSA, prostate specific antigen; PSCA, prostate stem cell antigen; ABCG2, a member of the ATP binding cassette (ABC) transporters; BCRP, breast cancer resistance protein; HSC, hematopoietic stem cells; DHT, dihydrotestosterone; HGF, hepatocyte growth factor; PR, progesterone receptor.

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addition to androgens, estrogens play key roles in prostate carcinogenesis and progression, although the mechanisms are not fully understood (Ellem and Risbridger, 2007; Hu et al., 2011; Leung et al., 2010; Nelles et al., 2011; Prins et al., 2007; Prins and Korach, 2008). In men, chronically elevated estrogens have been associated with increased risk of prostate cancer (Modugno et al., 2001) while in rodents, estrogens in combination with androgens induce prostate cancer (Bosland, 1996). It is recognized that age, race, genetics (family history), diet, and environmental factors can impact prostate cancer risk (Reuben et al., 2010). Endocrine disrupting chemicals (EDCs) are a class of environmental toxicants that interfere with endocrine signaling pathways. In addition to direct effects in adults, strong evidence indicates that developing tissues are particularly sensitive to EDCs and that early-life EDC exposures promote specific disorders in adults (Foran et al., 2002; Heindel, 2005), a phenomenon referred to as the developmental basis of adult disease.

Recent advances in stem cell research indicate that stem cells and early stage progenitor cells may be direct carcinogenic targets and the cells of origin in cancer initiation and progression. Together with our previous findings in animal models which show that early-life exposures to natural and environmental estrogens increase susceptibility to prostate carcinogenesis through structural and epigenomic reorganization (Ho et al., 2006; Prins, 1992; Prins and Birch, 1997; Prins et al., 1993, 1997, 2008, 2011; Prins and Ho, 2010), we hypothesize that developmental reprogramming of the prostate gland by EDCs may involve epigenomic alterations in prostate stem/progenitor cells during early gland formation, thus predisposing to prostate cancer upon aging. At present, there is a critical need to determine whether early life estrogenic reprogramming of prostate cells similarly occurs in humans. To meet this current need, we have recently developed novel *in vitro* and *in vivo* models using stem and early stage progenitor cells isolated from normal human prostates and used these to initiate hormonal carcinogenesis (Hu et al., 2011). Importantly, these *in vitro* prostasphere and *in vivo* chimeric prostate models with carcinogenic induction can serve as suitable models for examining stem cell perturbations and carcinogenic actions of EDCs on human prostate cells. In the current review, we will briefly assess available evidence for EDCs and increased prostate cancer risks, discuss recent advances in prostate stem cell research, and present evidence for reprogramming of human prostate stem/progenitor cells by estrogens and EDCs using our novel human prostasphere and chimeric prostate models.

2. Endocrine disruptors and prostate cancer risk

In the human population, direct connections between EDCs and prostate cancer are primarily limited to epidemiology studies and *in vitro* analysis using cancer cell lines (Prins, 2008). These findings are supported by *in vivo* studies in animal models that suggest associations between EDCs and prostate cancer, carcinogenesis and/or susceptibility. Herein we will highlight the evidence on EDCs with estrogenic actions. For the sake of simplicity, we here refer to environmental estrogens as molecules with identified estrogenic activity, mostly through activation of ERs or altered estrogen metabolism.

The most compelling data in humans to link prostate cancer with environmental chemicals comes from the established occupational hazard of farming and increased prostate cancer rates which is believed to be a function of chronic or intermittent pesticide exposures (Alavanja et al., 2003; Meyer et al., 2007; Morrison et al., 1993; Van Maele-Fabry et al., 2006). This is supported by a large epidemiology study (Agricultural Health Study) in a collaborative effort between the NCI, NIEHS and EPA (www.aghealth.org) that evaluated >55,000 pesticide applicators in North Carolina and Iowa since 1993 and revealed a direct link between methyl bromide exposure, a fungicide with unknown mode of action, and increased prostate cancer rates (Alavanja et al., 2003). Further, six pesticides (chlorpyrifos, fonofos, coumaphos, phorate, permethrin and butylate) out of 45 common agricultural pesticides showed correlation with exposure and increased prostate cancer in men with a familial history, suggesting gene-environment interactions (Alavanja et al., 2003; Mahajan et al., 2006). Significantly, chlorpyrifos, fonofos, coumaphos, phorate, permethrin are thiophosphates with acetylcholine esterase inhibitor action as well as significant capacity as p450 enzyme inhibitors. In particular, chlorpyrifos, fonofos and phorate strongly inhibit CYP1A2 and CYP3A4 which are the major p450s that metabolize estradiol (E2), estrone and testosterone in the liver (Usmani et al., 2003, 2006). This raises the possibility that exposure to these compounds may interfere with steroid hormone metabolism and disturb hormonal balance which in turn contributes to increased prostate cancer risk. A similar mechanism of endocrine disruption *in vivo* has been identified for polychlorinated biphenyls (PCBs) and polyhalogenated aromatic hydrocarbons (including dioxins, BPA and dibenzofurans) through potent inhibition of estrogen sulfotransferase which effectively elevates bioavailable estrogens in target organs (Kester et al., 2000, 2002).

Bisphenol A (BPA) is a high volume synthetic monomer used in the production of polycarbonate plastics, epoxy linings of food and beverage cans, and in numerous common household and consumer products. Significant levels of BPA have been found in the urine of 93% of US individuals (Calafat et al., 2008) with highest levels found in infants and children (Calafat et al., 2009; Eddington and Ritter, 2009; Kuroda et al., 2003; Lee et al., 2008). BPA was initially synthesized in the 1890s, however, its estrogenic actions of were identified in 1936 (Dodds and Lawson, 1936). Although its relative binding affinity and activation of nuclear ERα and ERβ are ~1000 to 10,000-fold lower than E2 or diethylstilbestrol (Kuiper et al., 1998; Lemmen et al., 2004), BPA activates membrane ERs through non-genomic signaling pathways with an EC_{50} equivalent to E2 (Song et al., 2002; Walsh et al., 2005). Effects of BPA with regards to carcinogenic potential, including the prostate gland, have been reviewed by an expert panel (Keri et al., 2007). In short, there is evidence from rodent models and human prostate cell lines that BPA can influence carcinogenesis, modulate prostate cancer cell proliferation and for some tumors with AR mutations, stimulate progression. Using rodent models, our laboratory has shown that transient, early-life exposure to low-doses of BPA increased susceptibility to adult-onset precancerous lesions and hormonal carcinogenesis. Specifically, neonatal rat exposure to 10 μg BPA/kg BW on post-natal days 1, 3 and 5 significantly increased the incidence and score of adult estrogen-induced prostate intraepithelial neoplasia (PIN), the precursor lesion for prostate cancer, as compared to control rats (Ho et al., 2006; Prins et al., 2008, 2011). This model of heightened sensitivity to hormonal carcinogenesis is relevant to humans in that relative E2 levels increase in the aging male and may contribute to prostate disease risk (Kaufman and Vermeulen, 2005). Furthermore, these studies identified alterations in DNA methylation patterns in multiple cell signaling genes in BPA-exposed prostates which suggest that environmentally relevant doses of BPA reprogram the developing prostate through epigenetic alterations (Ho et al., 2006; Prins et al., 2008).

PCBs are a class of synthetic, lipophilic, and persistent compounds widely used in the mid-20th century. Although now banned, the general population continues to be exposed to PCBs due to persistence, ubiquity in the environment, and bioaccumulation up the food chain. Measurable levels of serum PCBs are found in the majority of the general population (Patterson et al., 2009). Many PCBs have estrogenic or anti-androgenic activity and may

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