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Role of estrogens in development of prostate cancer

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Abstract

Estrogens have previously been extensively used in prostate cancer treatment. Serious side effects, primarily in cardiovascular system have, however, limited their use. The therapeutic effect of estrogen in preventing prostate cancer growth was mainly obtained indirectly by feedback inhibition of the hypothalamic release of LRH leading to lowered serum androgen levels and castration like effects.

Prostate tissue is also most probably a target for direct regulation by estrogens. Prostate contains estrogen receptor α (ERα) and β (ERβ), which are localized characteristically in stroma and epithelium, respectively. The physiological function of these receptors is not known but there is evidence of the role of estrogens in prostatic carcinogenesis. Developing prostate seems particularly sensitive to increased level of endogenous and/or exogenous estrogens. Perinatal or neonatal exposure of rats and mice to estrogens leads to "imprinting" of prostate associated with increased proliferation, inflammation and dysplastic epithelial changes later in life. Prolonged treatment of adult rodents with estrogens along with androgens also leads to epithelial metaplasia, PIN-like lesions and even adenocarcinoma of prostate speaking for the role of estrogen in prostate cancer development. Recent results concerning antiestrogen inhibition of prostate cancer development beyond PIN-type lesions in transgenic mouse models further suggests a role for estrogens in prostate cancer progression. These results also suggest that direct inhibition of estrogen action at the level of prostate tissue may provide an important novel principle of development of prostate cancer therapies.

Keywords: Estrogens; Prostate; Cancer

1. Introduction

Estrogens regulate the development and function of prostate at several stages of a man's life by indirect and direct mechanisms. Prostate growth, differentiation and function are primarily controlled by androgens but estrogens modulate these effects in several ways. The most important routes of indirect estrogen regulation are interference of androgen production by repression of the hypothalamic–pituitary–gonadal axis and direct effects on testis. Another important, indirect route for estrogen regulation of prostate is via prolactin. Estrogens also clearly have direct effects on prostate, which may be elicited by external hormone or by estradiol produced by local aromatisation of testosterone. It has been very difficult, however, to work out the mechanisms and the physiological importance of these effects.

Estrogen regulation has also been considered as one of the hormonal risk factors in association of development of benign prostatic hyperplasia and prostate cancer [1–3]. The evidence for the possible role of estrogen in prostate cancer has come from epidemiological and experimental studies. First, the epidemiological evidence includes a strong correlation of prostate cancer incidence with geographical location, which may be associated with dietary factors among other environmental influences and their endocrine consequences. The role of phytoestrogens and other dietary and environmental estrogens have particularly been considered [3]. The correlation of the levels of serum estrogen or estrogenic compounds with the prostate cancer incidence in various population groups has not, however, provided any conclusive evidence of the role of estrogens in explaining the differences in prostate cancer incidence in those groups [4]. Second, the serum estrogens are known to increase and androgens decrease upon aging, which changes precede or coincide with the increasing incidence of prostate cancer. The altered ratio of serum

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androgens to estrogens and progression of prostate cancer have been suggested to have a causal relationship with each other. However, despite extensive studies, there is no conclusive clinical evidence of a strong correlation between elevated serum estrogen or estrogen/androgen ratio and the increased incidence of prostate cancer [5,6]. Third, there is, however, strong experimental evidence that shows that excessive or untimely exposure to estrogens can facilitate development of prostatic changes, disorders and even malignancies [7]. These results open up a possibility for direct or indirect effects of locally produced estrogen [8].

The indirect estrogen effects were exploited for a long time as a therapy of prostate cancer [3,9]. Estrogen treatment was based on the primary observations of Huggins and Hodges [10] on estrogen regulation of prostate cancer [10,11]. As suggested in these original papers, the therapeutic effect of estrogen is primarily mediated by suppression of the hypothalamic–pituitary–gonadal axis and by direct effects on the Leydig cells in testis, which together lead to decreased serum levels of testosterone and castration like effects in prostate. In these studies estrogen was also suggested to have direct (then considered "toxic") effects on prostate [11].

Estrogen treatment was an effective form of therapy of advanced prostate cancer but unfortunately, it was associated with a high risk of serious cardiovascular complications, which eventually strongly limited its clinical use [9].

2. Biological effects of estrogens on prostate

2.1. In vitro effects of estrogen

The evidence for direct prostatic effects of estrogen comes mainly from studies with organ cultures of normal rat or human prostate or samples of human prostate cancer. In those studies estrogen was found to stimulate DNA synthesis and induce metaplastic epithelial morphology both in human and rat prostate [12,13]. Estrogen also regulated expression of prostate specific genes [12,14]. When estrogen was combined with androgen, the effects on DNA synthesis and specific gene expression were mainly synergistic but, interestingly, the induction of metaplastic changes was prevented [12,13] and the organized epithelial morphology largely maintained in the in vitro cultures.

2.2. Neonatal imprinting of prostate by estrogen treatment

Developing prostate seems to be particularly sensitive to the effects of estrogen. Prenatal or neonatal treatment of rodents with high doses of estrogen during the first 5 days after the birth, when tubular branching morphogenesis of prostatic organogenesis occurs leads to marked changes in prostate development and function later in life. This is invariably associated with hyperprolactinemia and hypoandrogenemia, which may explain a major part of the effects. A good example of permanent alterations induced by an early estrogen exposure is the rodent neonatal estrogenization model [15]. Neonatal estrogenization with estradiol or diethylstilbestrol (DES) results in time-of-exposure and dose-dependent inhibition of prostatic growth and function in mice and rats [16–19]. Besides growth inhibition, neonatal estrogenization promotes inflammation, epithelial hyperplasia and development of dysplastic lesions, which histologically resemble PIN-lesions [19,20]. Furthermore, the expression of several important growth-regulatory genes is altered. This includes upregulation of ERα and estrogen-responsive proto-oncogenes c-*myc* and c-*fos* [20–22] and downregulation of AR and ERβ [23,24].

Experiments with ER-deficient mouse models indicate that the effects induced by neonatal exposure to high doses of estrogen are largely mediated through stromal ERα. Neonatal exposure to DES fails to induce epithelial dysplasia in ERα-deficient (ERKO) mice, but not in ERβ-deficient (BERKO) mice [25]. Tissue recombinant studies further emphasize the central role of stromal microenvironment, and in particular the importance of the expression of stromal ERs and AR in estrogen–androgen-induced prostatic carcinogenesis [26].

Between the years 1940 and 1971, millions of women were prescribed DES during pregnancy. Consequently, there are millions of women and men who were exposed to DES prenatally (DES daughters and DES sons). The long-term adverse consequences in DES daughters have been well documented, but only few studies have addressed the possible long-term health effects in DES sons. With regard to cancer risk, there is no conclusive evidence for elevated risk at any organ site. Most studies have focused on testicular cancer, which, based on rodent studies would be one of the likely effects, but the association between prenatal DES exposure and testicular cancer in humans remains controversial [27,28]. No studies on the prostate cancer risk in DES sons have been published to date, and it is not known if the effects observed in rodent models are relevant for humans. However, it should be taken into account that prostate cancer is typically diagnosed later in life, and the DES sons are now only approaching this age.

2.3. Estrogen-induced prostate dysplasia and malignancy in rodents

Prolonged treatment of rodents with a high dose of androgen and estrogen together induces growth of prostate, epithelial metaplasia, stromal hypertrophy and a strong inflammatory reaction in stroma [29–32]. These effects may be largely caused by associated hyperprolactinemia since most of them are inhibited with bromocriptine [33–35]. However, high serum levels of estrogen and prolactin associated with very low testosterone levels in aromatase overexpressing transgenic mice (AROM+) [36] or in estrogen-treated hypogonagal (hpg) mice [37] did not induce prostatic hyperplasia emphasising the need for a combined action of androgen and estrogen at least at

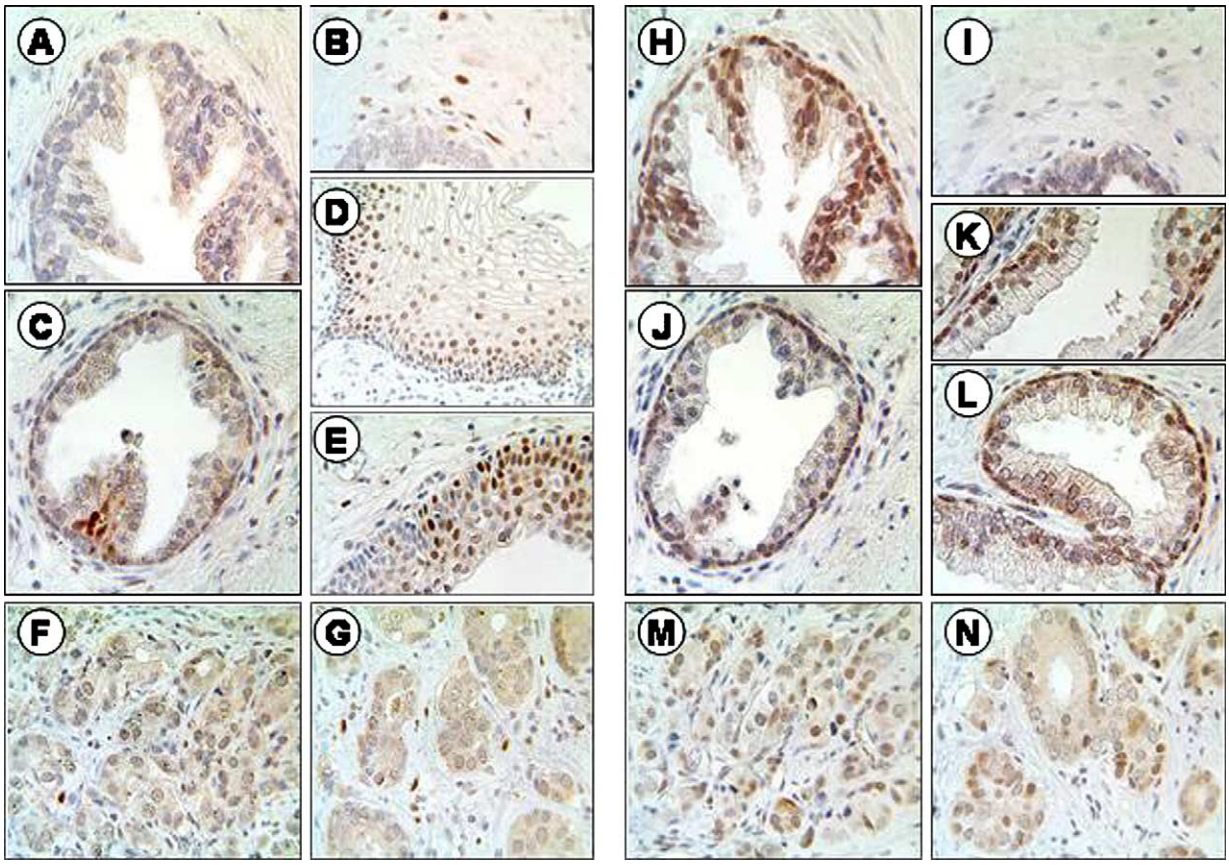

Fig. 1. Expression of estrogen receptors α and β (ERα and ERβ) in human prostate (A–E and H–L) and in prostate cancer (F and G, M and N). ERs were localized with immunostaining using ER-subtype-specific antibodies. Positive nuclei are indicated by brown color. Immunonegative nuclei show only the blue counterstain. Panel on left (A–G) shows localization of ERα, and panel on right (H–N) that of ERβ. In the peripheral zone (A, H, serial sections, K and L), majority of epithelial cells express ERβ (H, K and L), while ERα is not detectable (A). Serial sections from the central zone (B and I) demonstrate the presence of ERα-positive but ERβ-negative stromal cells. In glands/ducts with basal cell hyperplasia (C and J, serial sections), ERα is expressed in distinct groups of epithelial cells, while only modest ERβ expression is seen in basal cell layer. Very intense immunostaining for ERα is seen in the posterior wall of prostatic urethra showing squamous epithelial metaplasia (D), as well as the adjacent urothelium (E). In prostate cancer specimen, ERβ is present in some cancer cells, while others are negative (M and N). In the same cancer specimen, ERα was observed only in a small number of stromal cells (F and G).

some stage of prostatic development. In certain rat strains prostatic adenocarcinoma can be induced by a prolonged estrogen–androgen exposure, or with aromatizable androgen alone, but not with non-aromatizable androgen. These results imply that at least some prostatic effects of estrogen can be obtained by targeted aromatization of testosterone to estradiol [8] and further support the synergistic function of estrogens and androgens in prostatic carcinogenesis [38–40].

Lack of production of endogenous estrogen may also lead to development of prostatic enlargement in mice, as has been demonstrated in aromatase knockout (ArKO) mouse model [41,8]. With age, ArKO mice develop hyperplasia of epithelial, interstitial and luminal compartments, as well as up-regulation of androgen receptors. ArKO mice have significantly elevated serum androgen and PRL concentration, which may explain the enhanced prostatic growth. Interestingly, no induction of malignancy has been observed in ArKO mice, which again speaks for the critical role of estrogens in combination with androgen and possibly prolactin in the development of prostate cancer.

2.4. Role of prolactin in mediation of estrogen effects

Besides androgens, prostatic actions of estrogens are closely associated with those of prolactin [42]. Either pituitary-derived prolactin or prostate epithelium-produced endogenous prolactin [43] regulates prostate by stimulating its secretory activity, proliferation and survival [12,13,23,44–47]. Excessive prolactin stimulation induces hypertrophic changes in prostatic epithelium and stromal compartment in vitro in organ cultures [12,13] and in vivo in prolactin transgenic mice [48]. Similar results were also recently obtained with prostate-targeted prolactin transgenic mice [49]. Furthermore, molecular mimics able to block autocrine functions of prolactin reduced tumor formation and growth in nude mice [50]. These results together demonstrate that local endogenous prolactin is functionally important.

In rodents, estrogen triggers prostatic effects, which are very similar to those of prolactin [29,31]. Neonatal estrogenisation and prolonged treatments with androgen and/or estrogen are associated with periodical or persistent

hyperprolactinemia, which clearly mediates some of estrogen effects on prostate [31,33]. Such are, for example, development of dysplastic changes and accumulation of inflammatory and immune cells in prostatic stroma. Treatment with bromocriptine, an antagonist of hypothalamic L-dopa inhibiting prolactin release from pituitary, is able to prevent most although not all of estrogen effects [33,51,35].

In prostate epithelial cells estrogen increases the level of prolactin receptors [52]. It is not known whether estrogen regulates endogenous expression of prolactin by prostatic epithelial cells but in prostate-targeted prolactin transgenic mice the proportion of ERα expressing stromal cells is clearly increased and ERα is even expressed in some epithelial cells [49] resembling the situation in estrogen-induced squamous metaplasia changes of epithelium (Fig. 1). It is thus possible that prolactin mediates estrogen effects in prostate not only at the systemic but also at the cellular level as an important mechanism in estrogen-facilitated development of dysplastic changes in prostate [42].

3. Mechanisms of estrogen effect in prostate

3.1. Estrogen receptors in normal and cancerous human prostate

The presence of estrogen receptors in prostate suggests that estrogens may act directly on multiple sites in prostate. Interestingly, the two ER subtypes have very different expression patterns (Fig. 1). In human and rodent prostate, ERβ is the predominant ER subtype, expressed in the majority of the epithelial cells, as well as in some stromal cells (Fig. 1H–N). ERα is expressed in a more limited manner (Fig. 1A–G), and typically found in stromal cells only (Fig. 1B). However, ERα-positive cells are found in hyperplastic or metaplastic epithelium in the prostatic ducts and posterior periurethral region (Fig. 1C and J), but the functional relevance of this observation is still unclear. Based on the differential expression patterns of ERα and ERβ, it would be tempting to suggest specific roles for the two ER subtypes in the regulation of prostate growth and function in humans. However, at present, no such evidence exists, and the physiological roles of ER subtypes remain to be clarified.

ERβ is commonly expressed also in prostate cancer (an example in Fig. 1M, N and [53–56]) while ERα has been reported only in some studies [57]. Generally, the levels of ERα and ERβ in human prostate and prostate cancer seem to be very low at any stage of the disease when compared to breast cancer for example [56]. After the discovery of ERβ, there has been, however, considerable interest in its role during prostatic carcinogenesis and also in a possibility of using it as a prognostic marker but the results obtained have been rather conflicting. The studies by Horvath et al. [58] and Leav et al. [59] demonstrated reduction in ERβ expression during carcinogenesis, suggesting that ERβ might be important for the maintenance of normal prostate epithelium, but it is not yet known if reduction in ERβ expression is causally related to the development of neoplasia. The study by Horvath et al. [58] suggested that cancers retaining ERβ expression are associated with a higher rate of recurrence, and Leav et al. [59] reported that ERβ is expressed in prostate cancer metastases, which could indicate ERβ as a marker of highly malignant phenotype.

It is well known that multiple variant forms of ERβ are expressed in normal and cancerous tissues. The variant forms may functionally differ significantly from the "wild type" receptor. One such variant is ERβcx (also called ERβ2), which has structurally different ligand binding domain. It shows very poor ligand binding affinity to known estrogenic ligands, and has been suggested to act as an inhibitor of ERα action [60]. Interestingly, Fujimura et al. [61] reported that expression of wild type (wt) ERβ is lower in cancers than in the benign epithelium and inversely correlated with Gleason tumor grade. They also found that low wtERβ and high ERβcx expression are associated with poor cancer-specific survival. These results would suggest a shift from wtERβ to ERβcx during carcinogenesis, which would be consistent with the results of Horvath et al. [58] and Leav et al. [59] that did not differentiate between wtERβ and ERβcx.

Altogether, no clear association between ERβ expression and tumor grade or prognosis has been demonstrated so far as also concluded on the basis of recent studies using quantitative real-time RT-PCR [56].

3.2. ER-deficient mouse models

As expected, mice lacking functional ERs develop prostatic phenotypes (recently reviewed by Jarred et al. [62]). Obviously, because mice with prostate-targeted inactivation of ERs are not yet available, the phenotype is not necessarily caused solely by the lack of the receptor in prostatic tissue, but may also be secondary to the altered CNS-gonadal function. An example of prostate phenotype that is likely to be secondary to altered CNS-gonadal function has been observed in ERαKO (ERα-deficient) mouse. Couse and Korach [63] reported that ERαKOs develop enlarged prostates and seminal vesicles upon aging, without any pathological changes in the prostatic histology [25,64,65]. Serum testosterone levels in ERαKO males are twofold compared to WT littermates [66,67], and this could well explain the prostatic enlargement. Those mice do have, however, also increased serum estrogen levels.

On the other hand, the lack of functional ERα has also direct effects on prostate. It is well known that estrogen treatment induces development of squamous epithelial metaplasia in prostate, in particular at sites where the underlying stroma expresses ERα. This does not occur in ERαKO mouse, indicating that this specific response is ERα-dependent [65,62] and likely to be mediated by prostatic ERα. Squamous epithelial metaplasia has also been observed in human prostate, particularly in the posterior periurethral region (Fig. 1D), both in fetal prostate [68]

(possibly as a response to maternal estrogens), and in aging prostate [69–73]. Interestingly, human prostatic epithelium that is normally devoid of ERα (as in Fig. 1A), may express ERα (as in Fig. 1A), in ducts showing basal cell hyperplasia (as shown in Fig. 1C), as well as in the metaplastic epithelium in the posterior periurethral region (Fig. 1D and E) (also demonstrated by Adams et al. [68]). In addition, the epithelium in this site shows high expression of 17β-HSD type 1, the enzyme responsible for the conversion of estrone to estradiol [74]. Furthermore, a recent report also suggests an altered tissue localization of aromatase in prostate cancer compared to normal prostate [75]. These results further support the idea of regional differences in both estrogen production and responsiveness in prostate. Whether this relates in any way to the differences in the regional differences in the origin of prostate cancer remains to be explored.

Lack of functional ERβ may result in a very different prostatic phenotype. ERβ is normally expressed in the majority of the epithelial cells in rodent ventral prostate [76] but the specific functions of ERβ in prostate epithelium are not yet known. Weihua et al. [77] reported that aged ERβKO mice display hyperplastic foci and increased expression of proliferation marker Ki-67 in the ventral prostate. In contrast, in another ERβ-deficient mouse line, generated by Chambon and coworkers [78], no prostatic abnormalities were observed. At present, there is no explanation to this discrepancy.

4. Exploiting the pathways of estrogenic effects in inhibition of prostate cancer

4.1. Antiestrogen/SERM inhibition of progression of prostate cancer

The results on estrogen stimulation of prostatic proliferation, induction of prostatic dysplastic changes by neonatal estrogenisation or by a long-term treatment with estrogen in combination of androgen have led to several studies on the possibilities of inhibiting development and growth of prostatic malignancies by blocking estrogen action with antiestrogens [7]. Earlier studies with experimental models such as R3327 Dunning rat prostate adenocarcinoma [79] and Nb-2Pr-A tumor transplants in Noble rats [80] demonstrated partial growth regression by tamoxifen treatment. The clinical trials with a high-dose treatment with tamoxifen [81] or toremifene [82] were, however, disappointing. Although occasional positive effects were obtained the overall conclusion was that these antiestrogens used in breast cancer treatment did not produce any objective responses in advanced hormone-refractory prostate cancer.

Recent studies have, however, provided interesting new data that antiestrogens may effectively inhibit development and progression of experimental and even clinical prostate cancer. In a TRAMP transgenic mouse mode [83] toremifene decreased development of prostate tumors [84]. Even more interesting was that toremifene treatment also seemed to slow down and inhibit the appearance of high-grade prostatic intraepithelial neoplasia (PIN) lesions, which were found in placebo-treated transgenic mice. The possible mechanism was clearly different from indirect inhibition of androgen pathways. The level of serum estrogen was not essentially changed. These interesting results have led to clinical trials on the efficacy and safety of toremifene treatment of men with high-grade prostatic intraepithelial neoplasia [85,86]. As expected on the basis of past experience of using toremifene in treatment of breast cancer patients [87,88], the drug is well tolerated also in men [86]. The real clinical significance of these promising proof-of-concept type of observations in prevention of prostate cancer is now being investigated in a placebo-controlled, randomised long-term study [85].

Other antiestrogens such as trioxifene and raloxifene also retard growth or progression of prostate cancer in experimental models. Both decreased the metastatic speading of PAIII prostatic rat adenocarcinoma from primary tumors in Lobund–Wistar rats and increased the survival of the animals [89,90]. Raloxifene was also shown to induce apoptosis of both androgen dependent and independent prostate cancer cell lines in vitro [91].

The mechanisms of action of the antiestrogens in prostate cancer progression and metastasis remain to be studied. Toremifene is a chlorinated triphenylethylene derivative of tamoxifen, which is used in the treatment of patients with metastatic breast cancer [88]. It is a selective estrogen receptor modulator, which binds both estrogen receptors α and β and elicits antagonist effects at least in mammary gland and breast cancer cells and agonist effects in uterus, bone and liver [92]. Toremifene inhibits DMBA-induced tumorigenesis in mice and rats [87] inhibiting cell proliferation and inducing apoptosis [93]. The profile of prostatic actions of toremifene is not known. Based on the results concerning the requirement of stromal ERα for estrogen treatment-induced development of prostatic dysplasia or cancer one could hypothesise that it is this receptor isoform, which most probably mediates toremifene inhibition of development of high-grade PIN lesions and adenocarcinoma in TRAMP mice. Presently, it is not known, however, which are the gene targets and possible autocrine/paracrine mediators of this SERM action in prostate. Thus, it is not known, either, to which extent the tumor inhibitory effects of toremifene reflect its ability to counteract estrogen effects or its own characteristic SERM effects in prostate [92]. The analysis of the prostatic effects of recently reported ERα and ERβ specific ligands [94,95] and estrogen and toremifene target genes in the prostate of mice deficient in ERα or ERβ will be of great interest. Those studies will certainly provide information of the prostatic functions of ERα and ERβ and may also help in designing novel, prostate specific SERMs [96,97].

4.2. Role of phytoestrogens in the prevention of prostate cancer

Geographic differences in prostate cancer risk suggest that environmental factors may play a role in prostate carcinogen-

esis. More specifically, it has been suggested that dietary phytoestrogens, acting as "phytoSERMs" would, at least partly, account for the difference. Epidemiological studies show that phytoestrogen consumption and/or serum phytoestrogen concentrations are inversely correlated with prostate cancer risk [98,99]. Experimental studies support the idea of phytoestrogens as cancer protective agents: genistein (an isoflavonoid phytoestrogen) suppresses chemically induced prostate cancer [100] and reduces the incidence of poorly differentiated adenocarcinomas in TRAMP mouse model [101]. Furthermore, diet rich in isoflavonoid phytoestrogens inhibits or delays the development of DES-induced dysplastic lesions [102]. However, the beneficial effect of phytoestrogens in the prevention or treatment of human prostate cancer remains to be demonstrated. Only a very limited number of clinical trials has been carried out, suggesting a moderate favorable effect, but only in a small number of individuals [103,104].

5. Conclusive remarks

Experimental studies on prostate suggest that although inappropriate exposure to estrogens during the critical phase of differentiation and prostatic organogenesis or later in life may predispose prostate to development of abnormal changes estrogen may also have a role in progression of premalignant lesions to prostate cancer. Other results suggest that inhibition of pathways of estrogen effects may prevent this development, which opens up new possibilities of exploiting estrogen regulatory mechanisms in prostate along with other hormonal effectors, for therapeutic prevention of prostatic carcinogenesis and progression. To this end, information of prostate-specific mechanisms, signaling mediators and target genes of estrogen receptors would be urgently required.

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