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Sex steroid hormone metabolism and prostate cancer

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Abstract

The growth and function of the prostate is dependent on androgens. The two predominant androgens are testosterone, which is formed in the testis from androstenedione and 5α-dihydrotestosterone, which is formed from testosterone by 5α-reductases and is the most active androgen in the prostate. Prostate cancer is one of the most common cancers among men and androgens are involved in controlling the growth of androgen-sensitive malignant prostatic cells. The endocrine therapy used to treat prostate cancer aims to eliminate androgenic activity from the prostatic tissue. Most prostate cancers are initially responsive to androgen withdrawal but become later refractory to the therapy and begin to grow androgen-independently. Using LNCaP prostate cancer cell line we have developed a cell model to study the progression of prostate cancer. In the model androgen-sensitive LNCaP cells are transformed in culture conditions into more aggressive, androgen-independent cells. The model was used to study androgen and estrogen metabolism during the transformation process. Our results indicate that substantial changes in androgen and estrogen metabolism occur in the cells during the process. A remarkable decrease in the oxidative 17β-hydroxysteroid dehydrogenase activity was seen whereas the reductive activity seemed to increase. The changes suggest that during transformation estrogen influence is increasing in the cells. This is supported by the cDNA microarray screening results which showed over-expression of several genes up-regulated by estrogens in the LNCaP cells line representing progressive prostate cancer. Since local steroid metabolism controls the bioavailability of active steroid hormones in the prostate, the variations in steroid-metabolizing enzymes during cancer progression may be crucial in the regulation of the growth and function of the organ.

Keywords: Androgen; Estrogen; 17β-Hydroxysteroid dehydrogenaase; Prostate cancer

1. Introduction

Prostate cancer is one of the most common cancers among men and its incidence is increasing [1]. Despite the high prevalence and mortality rate of the disease, the mechanisms underlying the development and progression of prostate cancer are poorly understood. Androgens are necessary for the initiation of prostate cancer and the balance between androgen induced cell proliferation and apoptosis is thought to regulate the growth of the normal and cancerous prostate. In normal conditions a steady state exists between synthesis and inactivation of active androgens [2]. A change in the balance (increased synthesis, decreased inactivation) can lead to excessive androgen influence and increased cell proliferation.

The majority of prostate tumors arise from the secretory, androgen-dependent epithelial cells. The hormonal therapy used in the treatment of prostate cancer is based on the ablation of androgens in the circulation and prostate tissue by surgical or chemical castration. The hormonal treatment is in most cases initially effective but cancer cells usually lose their responsiveness to androgen ablation and begin to grow androgen-independently. Androgen withdrawal has been used in the treatment of prostate cancer patients since 1941 [3].

The principal circulating androgen is testosterone. In several androgen target tissues, like the prostate, testosterone is converted to 5α-dihydrotestosterone (DHT), which is the most potent natural androgen. Testosterone and DHT bind to an identical receptor, but they play distinct physiological functions. Testosterone regulates sexual differentiation and maintains libido and sexual functions, and DHT plays a major role in embryonic and pubertal external virilization [4].

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The results of epidemiological and experimental studies have suggested that estrogens could be involved in the induction of prostate cancer [5]. Estrogen receptor β has been suggested to play a role in the differentiation and proliferation of prostatic cells as well as possibly to modulate the initial phases of prostate carcinogenesis and androgen-independent prostatic growth [6]. However, despite the fact that estrogens have been used in the treatment of prostate cancer because of their negative feedback on the hypothalamic–pituitary–gonadal axis, the exact effects of estrogens on prostatic epithelium are still primarily unknown.

Prostate tissue contains also a variety of steroid-metabolizing enzymes required for the local formation of active androgens and estrogens from precursor steroids provided by the adrenals [7]. The main enzymes involved in local steroid metabolism are steroid sulfatases, 3β-hydroxysteroid dehydrogenases (3β-HSDs), 17β-hydroxysteroid dehydrogenases (17HSDs), 3α-hydroxysteroid dehydrogenases (3α-HSDs), 5α-reductases and aromatase (Fig. 1). The present review is mainly focused on the recent findings clarifying the role of 17HSDs in prostate cancer. In androgen and estrogen metabolism, 17HSDs catalyze the reactions between the active 17β-hydroxysteroids and less active 17-ketosteroids. Presently nine different 17HSD isoenzymes, types 1–5, 7, 8, 10 and 11 [8–10] have been characterized in humans. Types 1, 3, 5 and 7 are reductive enzymes, whereas types 2, 4, 8, 10 and 11 are oxidative enzymes.

2. Androgen metabolism in the prostate

The main circulating androgen, testosterone is synthesized in the Leydig cells of the testis from androstenedione (A-dione). The reaction is catalyzed by 17HSD type 3, under the control of pituitary hormones [11]. Conversion of A-dione to testosterone occurs to some extent also in the prostate but is catalyzed by a different enzyme, 17HSD type 5. In the basal cells of prostatic epithelium, the inactive precursor dehydroepiandrosterone (DHEA) is converted to A-dione by 3β-HSD1 and then to testosterone by 17HSD type 5 [12].

In the prostate, DHT is the predominant androgen and is formed from testosterone through the activity of 5α-reductase. Steroid 5α-reductases are microsomal NADPH-dependent enzymes, which act on steroid hormones with keto group at C3-position and a double bond between C4 and C5 in the structure. Two isoforms of 5α-reductases have been identified in several species including humans and named as type 1 and type 2 enzymes [13]. Both isoenzymes catalyze the same reaction but share only a limited degree of homology. The type 1 5α-reductase is most abundantly expressed in the hair follicle, the sebaceous gland of the skin and liver. The type 2 5α-reductase is expressed mainly in the prostate, the epididymis and the seminal vesicles [13].

In the prostate, DHT is also formed via oxidative type 3 3α-HSD (AKR1C2) activity, converting 5α-androstane-3α,17β-diol (3αA-diol) to DHT [14]. In a recent study it was found, however, that in cultured prostate cells AKR1C2 acts as a reductase eliminating DHT [15]. It was suggested that potent product inhibition by NADPH and oxidation of 3αA-diol to androsterone by 17HSD type 2 are possible reasons for the lack of DHT formation in the cells studied. Testosterone and DHT are mainly inactivated in the prostate by 17HSD type 2 to A-dione and 5α-androstanedione (5αA-dione), respectively [16]. DHT can also be reduced into 3αA-diol by 3α-HSD type 3 [14] or an estrogenic compound 5α-androstane-3β,17β-diol (3βA-diol) by 3β-HSD [14] or 17HSD type 7 [17].

3. Enzymatic characteristics and function of 17HSD type 1, type 2, type 5 and type 7

Human 17HSD type 1 and type 2 belong to the short-chain dehydrogenase/reductase (SDR) protein family. The main difference between the enzymes is the direction of their enzymatic activities. Human 17HSD type 1 mainly catalyzes

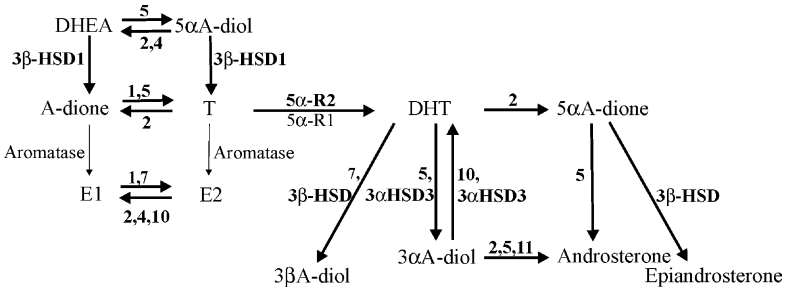

Fig. 1. Steroid metabolism in human prostatic tissue. 1, 2, 4, 5, 7, 10 and 11 are different 17HSD types; E1, estrone; E2, estradiol; A-dione, androstenedione; T, testosterone; DHEA, dehydroepiandrosterone; 5αA-diol, 5α-androstenediol; 5αA-dione, 5α-androstanedione; 5α-R1, 5α-reductase 1; 5α-R2, 5α-reductase 2; DHT, dihydrotestosterone; 3βA-diol, 5α-androstane-3β, 17β-diol; 3αA-diol, 5α-androstane-3α, 17β-diol; 3β-HSD1, 3β-hydroxysteroid dehydrogenase type 1. Androgens and estrogens are eliminated as sulfate or glucuronide derivatives.

reduction of estrone (E1) to estradiol (E2) [18], preferring the phosphorylated form of nicotinamide-adenine dinucleotide, NADPH, as a cofactor. In cultured cells, the human type 1 enzyme is also capable of reducing A-dione and 5αA-dione to some extent, but it clearly gives preference to phenolic substrates over androgens [19]. 17HSD type 2 predominantly catalyzes opposite reactions, converting estradiol to estrone, testosterone to A-dione, DHT to 5αA-dione and 20α-dihydroksyprogesterone to progesterone [20,21], and it acts most efficiently in the presence of the non-phosphorylated form of the cofactor NAD^+ [7]. Since intracellular concentrations of NADPH and NAD^+ are remarkably higher than those of $NADP^+$ and NADH, the preference of 17HSD type 1 towards reductive reactions and that of 17HSD type 2 toward oxidative reaction in vivo may be due to the cofactor specificities of the enzymes [7,22].

17HSD type 1 is an essential part of the estradiol production machinery in granulosa cells of the ovary [23,24] and syncytiotrophoblasts of the placenta [25,26], which secrete estradiol into the circulation. In addition, the type 1 enzyme contributes to the estrogen response by converting estrone to estradiol locally in certain targets of estrogen action, such as breast tissue [27,28]. In the prostate, 17HSD type 1 is expressed only in uroepithelial cells of the human prostate [16,29].

17HSD type 2 is involved in the inactivation of estradiol, testosterone and DHT and activation of progesterone. The type 2 enzyme may restrict the access of the active sex steroids into the circulation, and it may protect target tissues of hormone action against excessive sex hormone influence by catalyzing the conversion of androgens and estrogens into less active forms. 17HSD type 2 is expressed in a wide variety of tissues, such as breast, uterus, prostate, placenta, liver, intestine and kidney [8,9]. Typically, the type 2 enzyme is expressed in epithelial cells, such as the surface epithelial cells of the gastrointestinal and urinary tract [30,31].

17HSD type 5, a reductive 17HSD, is a member of aldo-keto reductase superfamily [32]. The enzyme catalyzes A-dione to testosterone and DHT to 3αA-diol and is expressed in the liver, prostate, adrenals, endometrium, mammary gland and ovary [33,34]. Recent studies have shown that the enzyme is the suppressor of nuclear receptor-regulated cell differentiation, and that progesterone and prostaglandin D_2 are the also substrates of 17HSD type 5 [32,33]. In addition, 17HSD type 5 has to some extent activity as a reductase of 3-keto and 17-keto steroids and as an oxidase of 3α- and 17β-hydroxysteroids [34].

Human 17HSD type 7 is a membrane-associated reductive enzyme converting estrone to estradiol and DHT to an estrogenic metabolite, 3βA-diol, thereby catalyzing the reduction of the keto group in either 17- or 3-position of the substrate. Minor 3β-HSD-like activities towards progesterone and 20-hydroxyprogesterone, leading to inactivation of progesterone by 17HSD type 7, was also detected [17]. Human 17HSD type 7 is expressed in steroidogenic and several peripheral tissues such as liver, lung, thymus and prostate. Its function is not known, but it may be responsible for the local production of estrogenic metabolites in peripheral tissues [17]. 17HSD type 7 may also have other substrates besides the sex steroids [35]. In a recent paper, it was shown that the enzyme acts as a 3-ketosteroid reductase in cholesterol biosynthesis converting zymosterone to zymosterol [36].

4. 17HSDs in the prostate

The presence of both reductive and oxidative 17HSD activities in the prostate tissue and separated epithelial and stromal components has been detected in several in vitro studies [37,38]. 17HSD activity has been detected principally in the epithelial compartment [37] but also the stromal component has both reductive and oxidative 17HSD activity [37,39]. Furthermore, prostatic 17HSD activity was found to be among the most abundant when compared with those of other tissue homogenates and the activities detected favored testosterone formation rather than that of A-dione [38]. In addition, relatively strong 17HSD activities have been measured in prostate cancer cell lines [40]. The main 17HSD activity detected in prostate epithelial cells in culture, PC-3 and LNCaP prostate cancer cell lines have been oxidative activity [40–42]. Our previous data have shown that of the 17HSD enzymes the type 2 enzyme is expressed in benign and malignant human prostate, and higher expression of 17HSD type 2 has been detected in benign prostatic hyperplasia compared with prostatic carcinoma [16]. In cultured cells the enzyme converts DHT and testosterone into their corresponding 17-keto derivatives. It was therefore suggested that the amount of active androgens in prostatic epithelial cells could be decreased by the local action of 17HSD type 2. Decreased local inactivation of androgens in the prostate could, therefore, shift the balance towards cell proliferation.

Androgen ablation therapy is one of the most widespread treatment strategies for prostate cancer. Tumors that survive long-term androgen withdrawal tend to be enriched for neuroendocrine cells [43]. Using LNCaP prostate cancer cells, we have developed a model to study mechanisms involved in the transition of prostate cancer to an androgen-independent stage [44]. In cultures without androgens, the androgen-dependent LNCaP cells are transformed into neuroendocrine cells, which further transform to androgen-independent highly proliferating granular and small round-shape cells (Fig. 2). During the process, LNCaP cells lose their ability to produce detectable amounts of androgen receptors and prostate specific antigen [44].

To get insight into changes in steroid metabolism during the cellular transformation, the conversion of several estrogenic and androgenic substrates into their specific products was investigated. The data indicate that the non-transformed LNCaP cells possess predominant oxidative 17HSD activity converting estradiol, testosterone and DHT into their less active 17-keto derivatives estrone, A-dione and 5αA-dione, respectively. At the androgen-independent transformed stage,

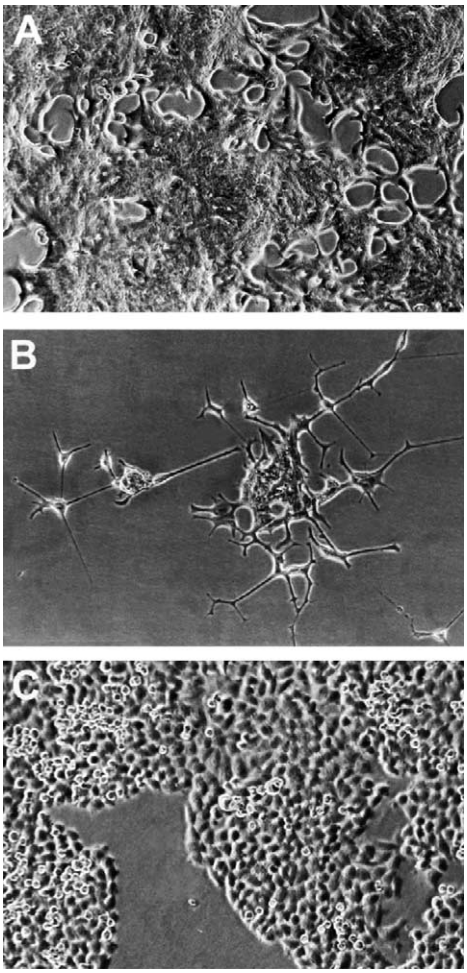

Fig. 2. Light microscopy images of morphological changes of LNCaP cells during the transformation. (A) untransformed cells; (B) neuroendocrine cells (C) transformed cells.

the oxidative activity was dramatically decreased and the LNCaP cells possessed remarkable reductive activity leading to the formation of estradiol and, to a lesser extent, testosterone. To get more information on the potential enzymes responsible for the oxidative and reductive activities, the expression levels of candidate genes, 17HSD types 2, 5 and 7, were determined. During the cellular transformation the relative expression of *HSD*17*B*2 gene decreased strongly. At the same time there was an increase in the expression of genes encoding 17HSD type 5 and type 7 [44]. The observed changes in 17HSD activities suggest that during transformation estrogen influence is increasing in the cells. This is supported by the cDNA microarray screening results which showed overexpression of several genes up-regulated by estrogens in the LNCaP cell line representing progressive prostate cancer and having further transformed into small aggressively-growing cells.

The observation of a remarkable decrease in oxidative 17HSD type 2 activity during cellular transformation is in line with our previous studies. We have identified in prostate cancer specimens at least three independent deleted regions at 16q, the most common being 16q24.1–16q24.2, which includes the gene for 17HSD type 2. The data further suggested an association between allelic loss at 16q24.1–16q24.2 and the clinically aggressive features of prostatic cancer [45,46]. In earlier studies, reduced expression of 17HSD type 2 mRNA has also been detected in prostate cancer specimens [16]. Further, down-regulation of *HSD*17*B*2 gene expression has been observed during progression of other forms of cancer, e.g. colon cancer [31]. During the disease progression, decreased inactivation of testosterone and DHT in the prostatic epithelium could shift balance toward increase in the proliferative pressure of cells and, furthermore, to unregulated prostatic growth.

Active steroid hormones are metabolized in peripheral tissues to inactive molecules, and for elimination from the body they are transformed to water-soluble forms. This is achieved by two major mechanisms forming sulphate or glucuronide derivatives of the steroids in conjugation reactions occurring at a hydroxyl group of the molecules. The glucuronidation is an important part in the inactivation and excretion of androgens. UDP-glucurosyltransferases are capable of inactivating testosterone, DHT, 3α-Adiol and androsterone to their respective glucuronides. Our recent results suggest that in LNCaP cells glucuronidation of androgens increases during the progression of the cells to androgen-independent state (unpublished data).

5. Conclusion

The prostate is an androgen-dependent organ. Androgens have been thought to play an important role also in prostate cancer development. While there is increasing indirect evidence for such involvement, direct evidence is still lacking. The possible role of other steroid hormones like estrogens in prostate cancer development is not yet elucidated. A balance exists between production and clearance of steroid hormones in human body. This is regulated by coordinated network of steroidogenic and steroid-metabolizing enzymes. Changes in the balance may be important in cancer development since hormones may act as carcinogens by increasing cellular proliferation and thereby increase the chance of random DNA copy errors. Using LNCaP cell line we have developed a cell model to study mechanisms involved in prostate cancer progression. Decreased inactivation of testosterone and DHT and increased production of estrogenic metabolites in the cells during the progression could shift balance toward increase in the proliferation. A better picture of molecular mechanisms in hormone biosynthesis and metabolism and changes in gene expression associated with altered hormone influence will help to understand better the roles of different hormones and their metabolites in prostate diseases.

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