Journal of Steroid Biochemistry & Molecular Biology 145 (2015) 164–171

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Reconsideration of progression to CRPC during androgen deprivation therapy

Atsushi Mizokami*, Mikio Namiki

Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Sciences, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8640, Japan

ARTICLE INFO

Article history:
Received 14 February 2014
Received in revised form 19 March 2014
Accepted 28 March 2014
Available online 6 April 2014

Keywords:
CRPC
DHEA
Androgen deprivation therapy
Mechanism

ABSTRACT

Androgen blockade-naïve prostate cancer (PCa) develops into CRPC during androgen deprivation therapy (ADT) by various genetic actions. The androgen-AR signaling axis plays a key role in this development. PCa cells mainly adapt themselves to the environment of lower androgen concentrations and change into androgen-hypersensitive cells or androgen-independent cells. Androgens of adrenal origin and their metabolites synthesized in the microenvironment in an intracrine/paracrine fashion act on surviving PCa cells and secrete prostate specific antigen (PSA). Total androgen deprivation (TAD) (castration, antiandrogen, and CYP17A1 inhibitor) can become an effective therapeutic strategy concerning the androgen signaling axis-related pathway. However, it is important to ascertain whether elevation of serum PSA results from AR activation or from an androgen-independent tumor volume effect. Then, clinicians can judge it adequately using the imaging studies such as CT or bone scan as well as PSA and bone metabolic markers, an approach which is necessary to judge which treatment is most suitable for the CRPC patients.

This article is part of a Special Issue entitled 'Essential role of DHEA'.

Contents

1. Mechanisms of progression into CRPC related to an androgen-independent pathway

Multiple molecular mechanisms which could account for the development of castration-resistant prostate cancer (CRPC) have been proposed [1] (Fig. 1). One mechanism is an androgen receptor (AR) – independent pathway. When we look at many published papers on the immunohistochemistry of AR, the AR expression level is heterogeneous in high Gleason grade prostate cancer (PCa) tissue [2]. Androgen-independent growth might result from clonal expansion of such androgen-independent cells at the latter stage [3]. Even if AR is expressed in PCa cells, other factors, such as BCL-2 and EZH2, might dominantly act on cell proliferation irrespective of androgen deprivation therapy (ADT) [4,5].

2. Mechanisms of progression into CRPC related to adrenal androgen precursors

Recent clinical evidences that CYP17A inhibitors and second generation antiandrogens are very effective in CRPC after docetaxel treatment have clearly proven that the androgen-AR signaling axis is an important pathway in the progression of PCa (Fig. 1) [6–8]. The evidence obtained indicates that alterations of AR itself, which is either absent or at low concentration in the original

* Corresponding author. Tel.: +81 76 265 2393; fax: +81 76 222 6726.
E-mail address: mizokami@med.kanazawa-u.ac.jp (A. Mizokami).

http://dx.doi.org/10.1016/j.jsbmb.2014.03.015
0960-0760/

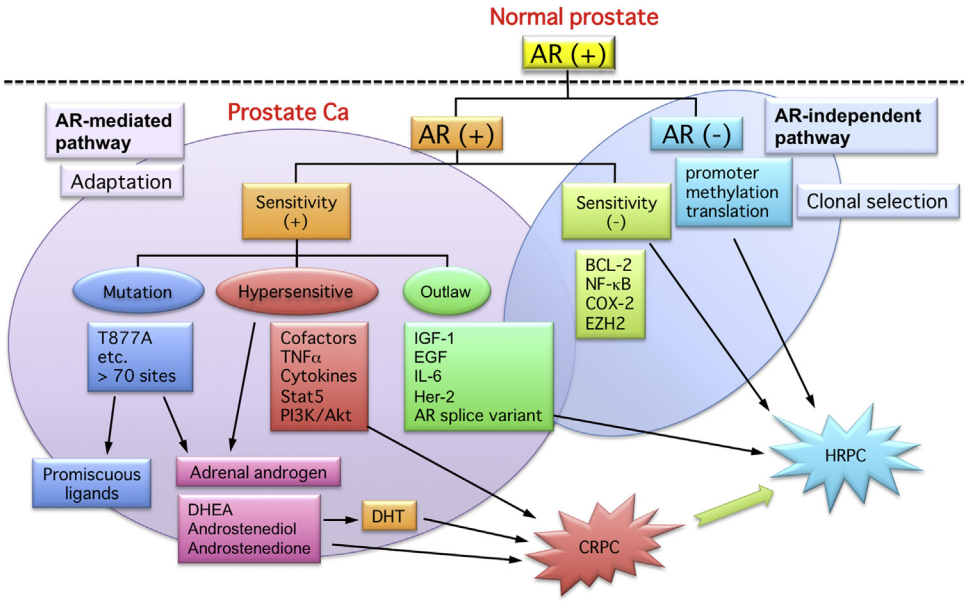

Fig. 1. Mechanisms of recurrence focusing on AR during ADT. Blue and purple shapes represent AR-independent pathway and AR-mediated pathways, respectively. The two pathways sometimes overlap.

androgen-dependent state, results in an androgen-hypersensitive situation where stimulation of PCa growth occurs at castrate levels of androgens [9,10]. One of the AR alterations is AR mutation that results in promiscuous ligand specificity [11]. Therefore, in addition to its normal ligands, namely testosterone (T) and dihydrotestosterone (DHT), both androstenediol, estradiol, and pregnenolone, a common precursor of many steroids, can activate the AR and stimulate the proliferation of LNCaP cells that have such a mutated AR [12–14].

Even if ADT is applied, the concentration of a precursor of T, namely androstenediol in PCa tissue is almost the same [14]. Once AR mutation occurs at T877A androstenediol will activate AR. The activation of AR is also a very critical factor for progression into CRPC. Overexpression of AR by gene amplification and enhanced transcription induces androgen-hypersensitivity [15,16]. AR coactivators such as TIF2 and ARA55 also enhance androgen-hypersensitivity [17,18]. Even if ADT decreases serum T to castration levels, androgen-hypersensitive PCa will adapt to the circumstance at the low level of T in serum, begin to reproduce, and secrete prostate specific antigen (PSA) again.

2.1. Synthesis of intratumoral androgens

Not only AR alteration that adapts to the circumstance at the low level of serum T occurs after ADT in PCa, but also residual androgens in PCa tissue and metastasis sites affect altered AR. However, physiological concentrations of the adrenal androgen precursors dehydroepiandrosterone (DHEA) cannot activate AR nor stimulate proliferation of PCa [14]. It is necessary for DHEA to be converted into T or DHT in order to activate AR. Interestingly, DHT is present in PCa tissue after ADT. Specifically, when PCa patients are treated with ADT, serum T and DHT decreases to less than one-tenth of pretreatment levels [19]. However, T and DHT in PCa tissue are still present at 20–40% of pretreatment values [14,19–23]. These residual androgens in PCa tissue after ADT continue to promote AR activation. This is accounted for by the observation that combination therapy with a LH-RH agonist, to block androgen production, and an antiandrogen, to block ligand binding to the AR, is more effective for PCa treatment than either therapy alone [19,24,25]. Moreover, recent clinical trials using abiraterone acetate for post-docetaxel chemotherapy revealed that CYP17 blockade by abiraterone acetate results in decline in PSA [26], suggesting androgen synthesis from adrenal precursors stimulates cancer progression even after docetaxel treatment.

T and DHT in PCa tissue after medical or surgical castration are synthesized locally in the prostate from DHEA of adrenal origin [14,19–23]. The metabolism from DHEA to DHT in peripheral target tissues depends upon the level of expression of various steroidogenic enzymes in the specific cell types of these tissues [27]. Adrenal DHEA is converted to T by 17β-hydroxysteroid dehydrogenase (HSD17B) and 3β-hydroxysteroid dehydrogenase (HSD3B). T is then converted to DHT by 5α-steroid reductase (SRD5A) in the prostate. HSD3B catalyzes almost exclusively the oxidation of 3-hydroxy-into 3-keto-5-androstene steroids (DHEA and 5-androstenediol are converted into androstenedione and testosterone by HSD3B, respectively) [28]. On the other hand, the HSD17Bs are responsible for the formation and inactivation of all active androgens: types 1, 3, 5, 7, 12 and 13 HSD17B catalyze the reductive reaction (DHEA and androstenedione are converted into androstenediol and T, respectively) while types 2, 4, 6 and 8 HSD17B catalyze the oxidative reaction (reverse conversion). SRD5A catalyzes the 5-reduction of 4-dione, T and other 4-ene-3-keto-steroids to the corresponding 5-dihydro-3-keto-steroids. These enzymes are localized in various peripheral tissues, including the prostate, with specific expression patterns in each tissue. For example, HSD3B and type 5 HSD17B were localized in basal cells of alveoli, stromal cells and endothelial cells of blood vessels of the prostate [29]. Various androgen-metabolising enzymes were also expressed in prostate cancer [30–33].

2.2. Alteration of androgen metabolism in PCa and CRPC

Fung et al. have observed increased expression of the androgen synthesizing enzyme AKR1C3 (type 5 HSD17B), in PCa tissue [34] while Stanbrough et al. confirmed that ADT-resistant PCa and bone marrow metastases expressed increased levels of multiple genes responsible for androgen metabolism (HSD3B2, AKR1C3, SRD5A1, AKR1C2, AKR1C1 and UGT2B15) [35]. Especially, the mRNAs encoding HSD3B2, AKR1C3, and SRD5A1 that can make DHT from DHEA were overexpressed by 1.8, 5.3, and 2.1-fold in CRPC, respectively.