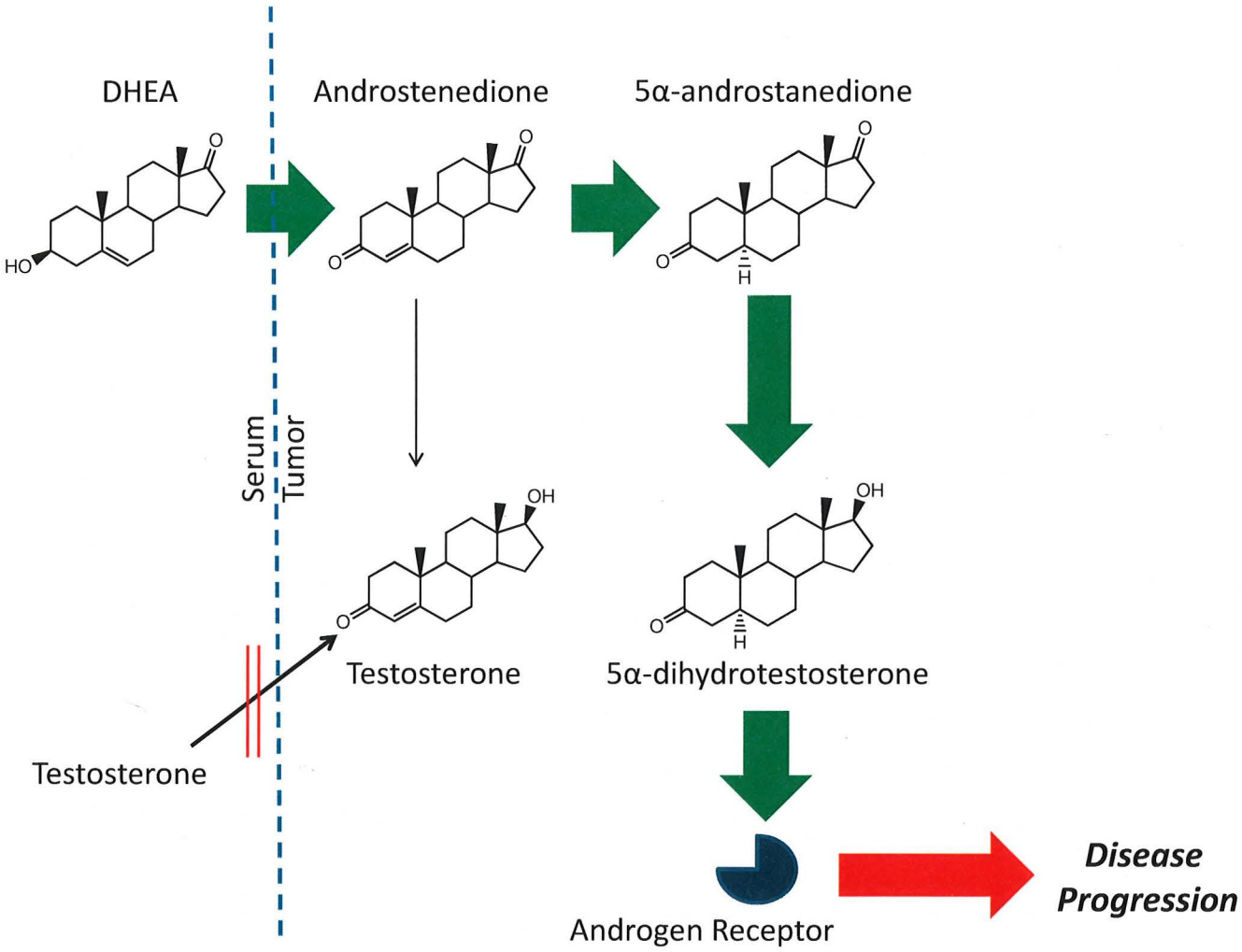
Hormonal therapy and resistance in prostate cancer



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Overview

Advanced prostate cancer is first treated with androgen deprivation therapy (ADT) by depletion of gonadal testosterone. Although the majority of patients typically have a favorable initial response, the benefit is almost always temporary and tumors typically progress after 12-18 months, as "castration-resistant" prostate cancer (CRPC). These tumors commonly remain dependent on androgen receptor (AR) function and become capable of synthesizing androgens from precursor steroids. The overall goals of our research program are to identify the mechanisms of CRPC and utilize the knowledge of these mechanisms to devise better treatments for men with CRPC.

Educational Objectives

1) Understand the treatment options for hormonal therapy of advanced prostate cancer
2) To become familiar with the limitations of standard hormonal therapy
3) Understand how knowledge of molecular mechanisms of resistance to hormonal therapy may lead to the development of improved treatment options

Introduction

Prostate cancer is the most common cause of non-skin cancer and second leading cause of cancer death in U.S. men, with nearly 241,000 new cases and 34,000 deaths estimated for 2011[1]. Just as the development of the normal prostate is dependent on the synthesis of androgens and expression of the androgen receptor (AR), the development and progression of prostate cancer is also dependent on the androgen axis[2]. In normal physiology, circulating testosterone undergoes conversion to 5α-dihydrotestosterone (DHT) in the prostate by steroid-5α-reductase-2 (SRD5A2)[3]. DHT binds AR, which undergoes nuclear translocation, and activates the transcription of hundreds of genes[4].

The essential role of AR and the androgen axis prostate cancer is illustrated in part by AR-driven oncogene expression and tumor progression through TMPRSS2-ETS translocations that occur commonly in prostate cancer[5]. With these translocations, the androgen-responsive regulatory region of TMPRSS2 is juxtaposed proximal to ETS family oncogenes around the time of local invasion, permitting AR-driven oncogene expression[6]. Inhibiting the androgen axis would therefore be expected to block oncogene expression and tumor progression.

Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) with gonadal testosterone depletion is the frontline treatment for advanced prostate cancer and may be accomplished by medical or surgical castration.[7] ADT also has clinical benefit for men with high risk or locally advanced disease undergoing radiation therapy or as an adjuvant for men who have undergone radical prostatectomy with lymph node involvement[8]. Of the ~ 2 million men currently diagnosed with prostate cancer in the United States, over one-third have received treatment with ADT[9].

Recognized limitations in measuring serum testosterone exist[10]. Nevertheless, a total testosterone concentration > 300 ng/dl (10.4 nmol/l) is generally considered normal[11]. The upper limit of castration concentrations of serum testosterone is considered to be 50 ng/dl (1.7 nmol/l), although lower concentrations (20 ng/dl; 0.7 nmol/l) are probably more desirable for optimal therapy[12]. Testosterone itself is an AR agonist.

However, testosterone is also converted in the prostate by SRD5A isoenzymes to DHT[13], which is a more potent AR agonist and is required for prostate development[14]. To effectively treat prostate cancer, the decline in serum testosterone with ADT must translate to decreased intraprostatic androgens. However, despite the ~94% decline in serum testosterone with ADT, intraprostatic concentrations of testosterone and DHT only decline by 70-80%[15]. The correlation of serum dehydroepiandrosterone (DHEA) with residual intraprostatic testosterone and DHT suggests an adrenal origin for androgens remaining in the prostate after ADT. Therefore, despite the clinical effects of ADT, the potential exists to intensify the effects of ADT on prostate tissue.

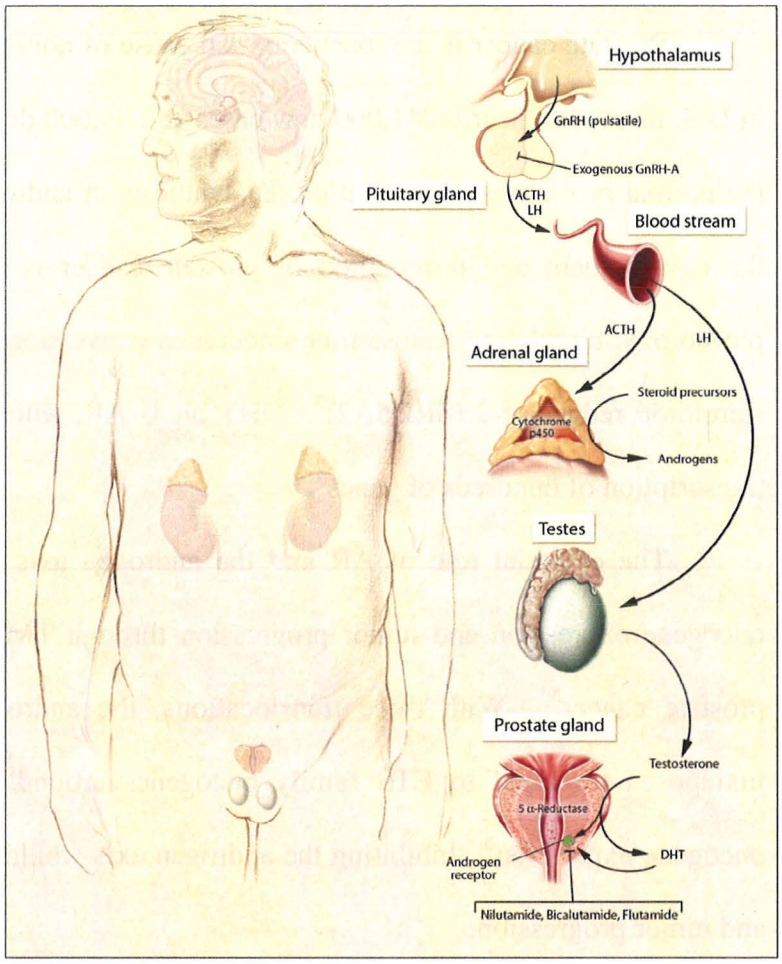

Figure 1. Endocrine axis and hormonal interventions in prostate cancer. Pulsatile GnRH physiologically stimulates LH release, which in turn stimulates testosterone release from the testes. Testosterone can therefore be blocked by GnRH-agonists or –antagonists. Testosterone is converted by 5α-reductase to DHT, which binds the androgen receptor (AR). Nilutamide, bicalutamide and flutamide are competitive AR antagonists. The adrenal gland synthesizes and releases androgen precursors, mainly in the form of DHEA and DHEA-sulfate. Cytochrome (CYP17A1) inhibitors block the synthesis and release of these precursor steroids.

ADT may be administered pharmacologically by medical castration or through surgical orchiectomy (**Figure 1**). Although medical castration is generally favored by patients because of its irreversible nature and psychological effects, bilateral orchiectomy is significantly less expensive[16, 17]

The major mechanism of the various means of medical castration is suppression of luteinizing hormone (LH) release from the anterior pituitary. Gonadotropin-releasing hormone (GnRH) is a peptide hormone synthesized in the hypothalamus and regulates pituitary LH release. Stimulation of LH release occurs only with pulsatile GnRH activity[18]. GnRH agonists and antagonists alike ablate physiologically pulsatile stimulation, blocking LH release into circulation and testosterone secretion from the Leydig cells of the testes that normally occurs.[19, 20]. Leuprolide, buserelin, goserelin and histrelin are synthetic GnRH agonists and are commonly used

for ADT. A potential disadvantage of GnRH agonists is an initial rise in serum testosterone on initiation of therapy and a potential for inducing a consequent stimulation of prostate cancer growth. However, the effects of the testosterone surge on tumor can be blocked by administration of an AR antagonist[21]. The use of a GnRH antagonist is an alternative to GnRH agonists and in contrast is not associated with a testosterone surge[20].

Resistance to ADT

The response to ADT in metastatic disease typically lasts 14-20 months by older radiographic criteria[22, 23]. However, the time to first rise in prostate-specific antigen (PSA), which is an androgen-responsive gene, is typically shorter and in modern practice usually first heralds the development of resistance. Tumor progression in the face of ADT is termed "castration-resistant" prostate cancer (CRPC). The previously used label of "androgen independent" prostate cancer is no longer favored because it is now clearly evident that this disease state is not truly independent of androgens[24, 25]. Several lines of evidence support the observation that a major contributor to progression from castration-responsive to CRPC occurs by a gain-of-function in AR[26]. First, the expression of PSA and other AR-responsive genes is restored in CRPC. Second, mutations occur in the AR ligand-binding domain that broaden specificity, permitting other steroids to bind AR and also converting the action of AR antagonists to agonists. Third, AR undergoes gene amplification in CRPC but not in tumors that are naïve to hormonal therapy. Fourth, a host of different growth factors, receptors and other intracellular signaling pathways have been implicated in "ligand-independent" or "ligand-sensitizing" action on AR. Fifth, an alteration in expression of nuclear receptor coactivators and corepressors has been reported to lead to increased AR-dependent transcription. Sixth, a constitutively active truncated AR variant that lacks the ligand binding domain has been reported to be expressed in CRPC. Finally, concentrations of intratumoral testosterone and DHT in CRPC have been shown to be present at levels sufficient to bind and activate AR[25, 27-29]. The main focus of the remainder of this protocol is on the last mechanism, which has been best validated clinically, and the therapeutic implications thereof.

CRPC Generates Its Own Androgens

The first studies suggesting that intraprostatic or intratumoral DHT is present at biologically significant concentrations were done over 30 years ago by Dr. Jack Geller[30]. Greater attention to this area was later given, probably in part due to the development of AR antagonists and the observed clinical activity that was presumed due to the displacement of residual androgens from the AR ligand binding domain[31, 32]. In the past decade, others groups have followed up on Geller's work. First, testosterone and DHT concentrations were assessed and found to be elevated by mass spectrometry in locally recurrent CRPC[33]. A subsequent study in metastatic CRPC tissues from a "warm autopsy" series yielded similar results[34]. Together, this body of literature demonstrates a clear and consistent picture of intratumoral steroidogenesis in CRPC that appears to be responsible for sustaining tumor progression.

Secondary Hormonal Therapies

AR antagonists are orally administered drugs that may be used upfront with ADT for "combined androgen blockade", or are alternatively used as secondary hormonal therapies after progression to CRPC[35, 36]. Steroidal AR antagonists including cyproterone acetate and megestrol acetate block AR function; however, they also have adverse effects due in part to nonspecific activity against other nuclear receptors[37]. In contrast, bicalutamide, nilutamide and flutamide are nonsteroidal AR antagonists used in current clinical practice, more selectively bind AR and have more favorable adverse effect profiles. Of the three, bicalutamide has the highest affinity for AR, though it remains considerably lower than that of DHT[38].

The human adrenal gland synthesizes abundant 19-carbon androgen precursors found in serum that contribute to the biology of prostate cancer. In human serum, DHEA is found at concentrations ranging from 5-20 nmol/l and conjugated DHEA in the form of DHEA-sulfate (DHEA-S) is much more abundant, being present at micromolar concentrations[39]. Ketoconazole is an antifungal imidazole, inhibits several CYP enzymes including 17α-hydroxylase/17,20-lyase (CYP17A1), which is required for the synthesis of all androgens and estrogens[40, 41]. In eugonadal males, inhibition of androgen synthesis leads to declines in serum T in the span of

a few hours and in CRPC leads to 50% PSA declines in about half of treated patients[40, 42]. Potential drawbacks of ketoconazole are probably due in part to inhibition of CYP enzymes other than CYP17A1 and include the potential for rhabdomyolosis[35].

Abiraterone Acetate

CYP17A1 enzymatic activity is absolutely required for the conversion of 21-carbon steroids to 19-carbon androgens, no matter the specific pathway(s) taken to intratumoral testosterone and DHT. Abiraterone acetate is a potent inhibitor of both CYP17A1 hydroxylase and 17,20-lyase activity[43]. The initial clinical studies of abiraterone acetate demonstrated declines in serum testosterone and androstenedione (AD) concentrations; however, pituitary compensation by luteinizing hormone hypersecretion resulted in some recovery of gonadal testosterone in males who were initially eugonadal[44]. In phase I/II trials of abiraterone acetate in men with CRPC, PSA declines greater than 50% occurred in approximately two-thirds of patients who had not been previously treated with chemotherapy[45, 46]. Pretreatment concentrations of DHEA, DHEA-S and AD in serum were associated with treatment response[45]. In a phase III trial of abiraterone acetate plus prednisone versus placebo plus prednisone in patients with docetaxel-treated CRPC, overall survival was 3.9 months longer in the abiraterone acetate-prednisone group[47]. Progression-free survival, PSA response rate and time to PSA progression were all found to be in favor of the abiraterone acetate-prednisone group. Based on these data, abiraterone acetate was approved by the United States Food and Drug Administration in April 2011 for the treatment of metastatic CRPC in men who had received prior docetaxel treatment. A second phase III trial of the same treatment groups is ongoing in men with CRPC not previously treated with docetaxel. Accrual has closed and results are soon anticipated. If this trial is positive, the favored standard of care would likely move treatment with abiraterone before commencement of chemotherapy.

MDV3100

A pitfall of the competitive AR antagonists used in current clinical practice is that the binding affinity for all of them is much poorer than DHT. Of these three drugs used currently, bicalutamide has the highest binding affinity. MDV3100 is a diarylthiohydantoin second-generation AR antagonist that has a five- to eightfold greater affinity for AR when compared to bicalutamide and is only two- to threefold lower than DHT in a competition assay[48]. MDV3100 potently excludes AR from the cell nucleus and suppresses AR chromatin occupancy on PSA and TMPRSS2 enhancers and induces better tumor responses in xenograft models of CRPC compared to bicalutamide. In a phase I/II clinical trial in patients with CRPC, PSA declines of 50% occurred in 57% of patients not previously treated with docetaxel and 45% of patients previously treated with docetaxel[48, 49]. Two placebo-controlled phase III trials of MDV3100 for metastatic CRPC are underway, both for docetaxel-treated and docetaxel-naïve patients. The docetaxel-treated trial has closed to accrual and the trial for docetaxel-naïve patients is currently accruing, including UT Southwestern as a participating institution. Multiple clinical trials over the span of decades have compared treatment using AR antagonists upfront along with the initiation of ADT (combined androgen blockade) with ADT alone and together have suggested minimal benefit for the upfront addition of AR antagonists[50]. However, this issue and benefit of combined androgen blockade versus ADT alone will probably be re-evaluated with the development of more potent AR antagonists, including MDV3100.

Origins of DHT in CRPC

At least two possible sources exist for the source of DHT in CRPC. Some reports suggest that DHT undergoes *de novo* synthesis all the way from cholesterol in the tumor[51]. However, DHEA and DHEAS from the adrenals are generally found abundantly in the serum. That *de novo* steroidogenesis requires 7 enzymatic steps and DHEA only 3 steps en route to DHT, the abundance of serum DHEA and the consequent relative efficiencies of flux through these two pathways together suggest that the adrenals are the main source of intratumoral DHT in CRPC[52].

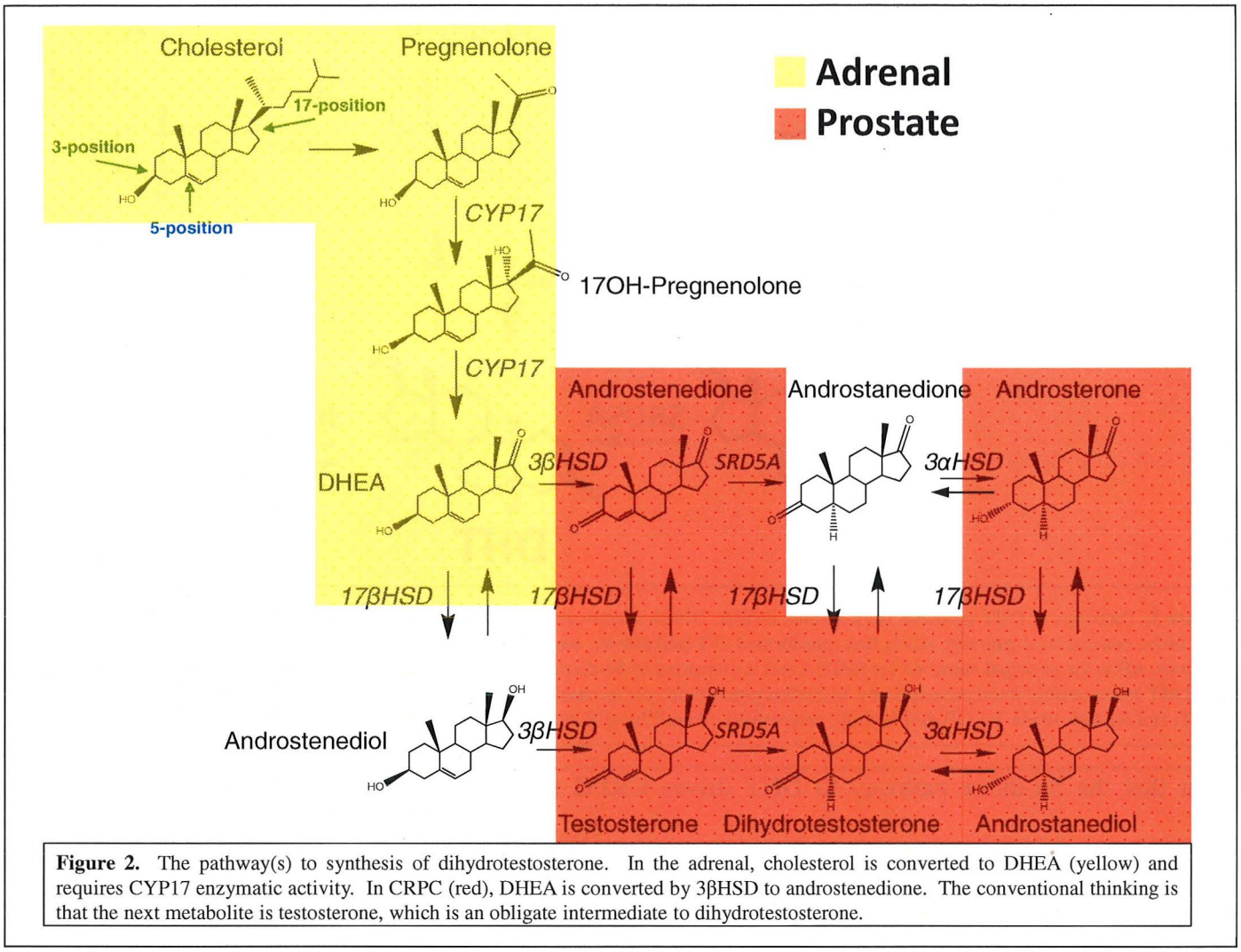

Figure 2. The pathway(s) to synthesis of dihydrotestosterone. In the adrenal, cholesterol is converted to DHEA (yellow) and requires CYP17 enzymatic activity. In CRPC (red), DHEA is converted by 3βHSD to androstenedione. The conventional thinking is that the next metabolite is testosterone, which is an obligate intermediate to dihydrotestosterone.

In CRPC, DHEA is converted by 3β-hydroxysteroid dehydrogenase/isomerase (3βHSD) to androstenedione[53]. The conventional thinking, as depicted in most all reviews in the field, is that androstenedione is then converted to testosterone, which is an obligate intermediate metabolite and undergoes 5α-reduction to DHT (**Figure 2**)[25, 26, 54]. Independent groups have shown that the expression of SRD5A-isoenzyme-1 (SRD5A1) increases in the transition from hormone-naïve prostate cancer to CRPC[34, 55]. This is generally interpreted to infer the requirement of SRD5A1 for the conversion of testosterone to DHT in CRPC.

An alternative possibility to the conventional thinking is that androstenedione undergoes 5α-reduction to 5α-androstanedione (5α-dione), which is then converted to DHT (**Figure 3**). We have recently shown that this alternative, the 5α-dione pathway, is the dominant pathway in all cell line models of CRPC tested and tumor/stromal co-cultures[56]. Two patients with metastatic CRPC underwent CT-guided biopsy and the results clinically confirm that the 5α-dione pathway is the dominant pathway in patients. Mouse xenograft experiments

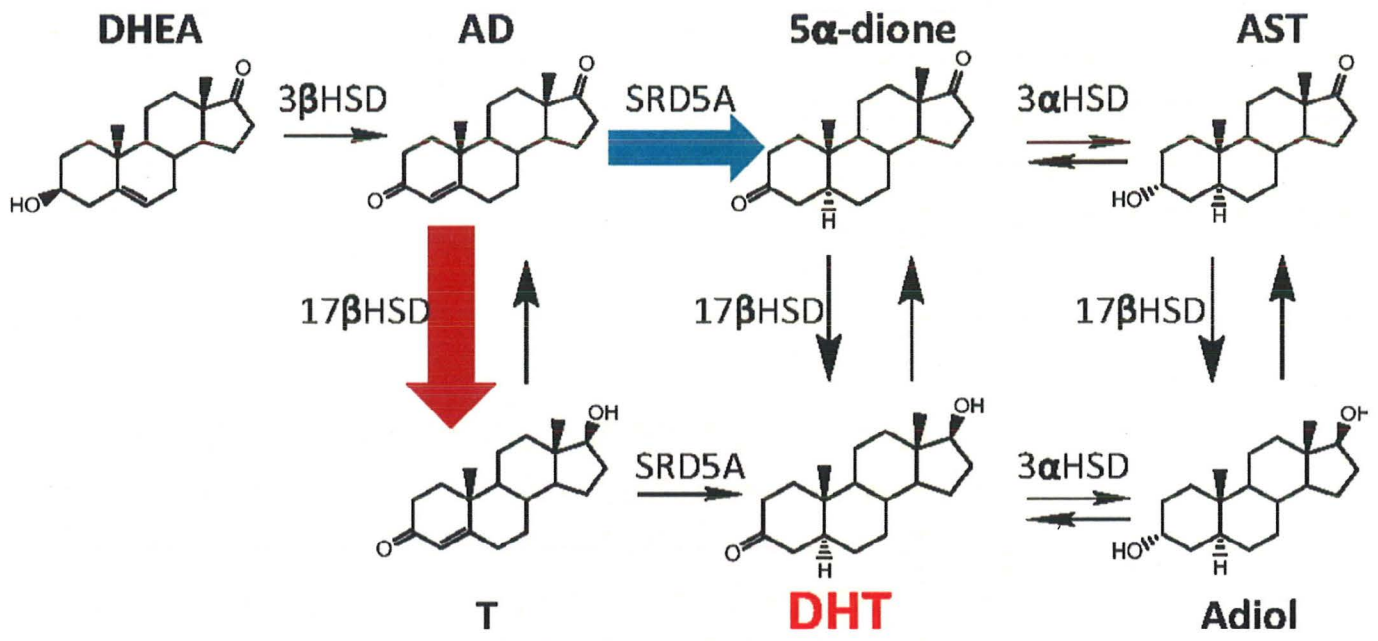

Figure 3. Pathways of DHT synthesis from adrenal DHEA. DHEA is converted by 3β-hydroxysteroid dehydrogenase/isomerase (3βHSD) to AD. In the conventional pathway, AD is first transformed to T (red arrow), which is then converted by SRD5A to DHT. In the alternative pathway, AD is the principal substrate for SRD5A and is converted to 5α-dione (blue arrow), a necessary precursor to DHT. Both 5α-dione and DHT are reversibly interconvertible by 3α-hydroxysteroid dehydrogenases (3αHSD) to the other 5α-reduced steroids, androsterone (AST) and 5α-androstane-3α,17β-diol (Adiol), respectively (from Chang K et al. *PNAS* 2011;108:13728-13733).

suggest that the 5α-dione pathway to DHT drives CRPC tumor progression. Furthermore, gene silencing experiments using shRNAs show that SRD5A1 is the isoenzyme required for the 5α-dione pathway. These findings have broad implications for determining mechanisms of resistance to hormonal therapies for CRPC, as well as the development of new therapeutic agents[57]. For example, studies of abiraterone acetate treatment in patients that determine residual intratumoral or tumor microenvironment androgens by assessing testosterone probably do not study the dominant intermediate steroid en route to DHT[58]. Furthermore, the finding that DHT is derived independent of testosterone may suggest that instead of blocking the conversion of androstenedione to testosterone, moving upstream to pharmacologically inhibit 3βHSD may be a logical point for therapeutic intervention[56].

Conclusions

1) ADT with depletion of gonadal testosterone is upfront therapy for advanced prostate cancer but does not completely ablate intratumoral DHT
2) Tumor progressing despite ADT as "castration-resistant" prostate cancer is not "androgen independent"
3) Other hormonal therapies block the synthesis of residual androgens or directly and competitively block AR
4) Intratumoral DHT synthesis does not follow the pathway of normal male physiology that goes through testosterone

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