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Review

Steroid biosynthesis and prostate cancer

Nima Sharifi [a], Richard J. Auchus [b,*]

[a] Division of Hematology/Oncology, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States
[b] Division of Metabolism, Endocrinology, and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States

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ABSTRACT

The pathways of androgen biosynthesis in human beings have been studied for decades, and the major pathways and enzymes responsible for testosterone and dihydrotestosterone synthesis are now well described. Minor or alternate pathways, which might contribute substantially to androgen production in specific states, have also emerged. Likewise, the requirement of androgen for prostate formation and growth date back over a half-century, and the dependence of prostate cancer on androgens has been known and exploited for as long. Despite the success of testicular removal or suppression, androgen receptor antagonists, and androgen synthesis inhibitors in the treatment of prostate cancer, the sources of androgen, their routes of synthesis, and the contributions of various routes remain topics of debate, particularly in castration-resistant disease when circulating androgens are very low. Here we review the major pathways of 19-carbon steroid synthesis in the adrenal and gonad, peripheral pathways to active androgens, and recent data charting flux of androgen precursors in prostate cancer. We are far from a unified understanding of androgen generation in prostate cancer, but the similarities and differences from glandular androgen synthesis that have already emerged provide important clues to designing the next generation of treatments for this common and devastating disease.

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Contents

1. Introduction

In an era before chemotherapy, when cancer treatment options consisted of surgical excision and field radiation only, Huggins and Hodges made the landmark observation that orchiectomy caused regression of metastatic prostate cancer [1]. Their discovery, which was recognized with the Nobel Prize for medicine in 1966, demonstrated that nearly all prostate cancers require circulating androgens for survival and progression. These responses, even when dramatic, were usually transient, and most eventually progressed as castration-resistant prostate cancer (CRPC), which was uniformly fatal. Over two decades later, the intraprostatic conversion of testosterone (T) to 5α-dihydrotestosterone (DHT) was characterized [2], and these experiments established the importance of DHT in prostate development. The singular requirement for DHT was verified genetically by the hypoplastic prostate tissue in patients with steroid 5α-reductase type 2 (SRD5A2) deficiency [3,4]

* Corresponding author. Address: MEND/Internal Medicine, University of Michigan, 5560A MSRBII, 1150 W. Medical Center Drive, Ann Arbor, MI 48109, United States. Tel.: +1 7347647764; fax: +1 7349366684.
E-mail address: rauchus@med.umich.edu (R.J. Auchus).

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and pharmacologically by the efficacy of 5α-reductase inhibitors in treating benign prostate hyperplasia [5]. Significantly, the presence of the crucial 5α-reductase enzyme in prostate cells themselves demonstrated that prostate epithelial cells actively contributed to the generation of their major trophic hormone. Subsequently, T-to-DHT conversion was confirmed in prostate cancer cell lines [6], and the striking preservation of intracellular DHT in these cancers suggested that mechanisms to maintain androgen stimulation were responsible for disease progression after castration [7].

Over the ensuing decades, less invasive approaches to androgen deprivation therapy (ADT) evolved, including estrogens (diethylstilbestrol, DES) and progestins [8], long-acting gonadotropin-releasing hormone (GnRH) agonists (leuprolide acetate, goserelin, etc.) [9], and the GnRH antagonist degarelix [10]. Androgen receptor (AR) antagonists or selective modulators (flutamide, bicalutamide, and nilutamide) showed some capacity to improve the disease even when circulating androgens were "suppressed" [11], suggesting that residual androgens somehow persisted in the prostate cancer despite treatments that lowered T and DHT production to below the limits of standard assays. Over the last 4 years, the therapeutic efficacy of abiraterone acetate, a 17α-hydroxylase/17,20-lyase (CYP17A1) inhibitor, confirmed that CRPC continues to be driven by AR activation [12]. In these trials, circulating T was lowered an order of magnitude beyond "suppressed" values with GnRH agonist to <1 ng/dL (<0.24 nmol/L) using an ultrasensitive tandem mass spectrometry assay, and integrated androgen metabolites in urine were lowered by >90% of baseline values [13]. In addition, trials with MDV3100, a next-generation AR antagonist, also showed improved survival in CRPC patients [14]. These recent advances have begged the questions: "how low is low enough (for T and DHT), what should we be measuring to assess ADT, and where are the residual androgens coming from?" These questions, in turn, have spawned a flurry of activity in understanding steroid biosynthesis in patients with CRPC and within the cancers themselves.

2. Physiology and feedback

All steroid hormones are derived from 27-carbon cholesterol, and a small repertoire of enzymes systematically oxidizes this carbon framework to 21-carbon steroids (including progestins, glucocorticoids, and mineralocorticoids), then 19-carbon steroids (androgens) and finally 18-carbon steroids (estrogens). The cleavage of cholesterol to pregnenolone—in amounts sufficient to contribute to circulating concentrations—occurs only in two tissues in adult males: the adrenal cortex and the testicular Leydig cells. Downstream enzymes tailor the biosynthetic pathways to yield the specific product of each steroidogenic cell type. In the circulation, steroids are heavily bound to plasma proteins, and the unbound hormones undergo uptake into target tissues, activation or inactivation by peripheral enzymes, and excretion, mainly in the urine. To understand steroidogenesis in prostate cancer and the logic behind current therapies, it is useful to first review adrenal and gonadal physiology [15].

The hypothalamic–pituitary–gonadal axis is governed by pulses of GnRH, released from its neurons in the arcuate nucleus of the hypothalamus every 90–120 min. Each pulse of GnRH results in a subsequent pulse of luteinizing hormone (LH) as well as follicle-stimulating hormone (FSH) from the pituitary gonadotropes. LH stimulates T production from the testicular Leydig cells, as well as a small amount of estradiol (E2). Both T and E2 (as well as DHT and progestins) provide negative feedback at the hypothalamus and pituitary to suppress LH and T production. The precise pulsatile rhythm of GnRH release is essential for LH release, and desensitization occurs with continued GnRH stimulation. This phenomenon is the basis for LH and T suppression with long-acting GnRH agonists following the initial rise or "flare" of these hormones.

Similarly, corticotropin-releasing hormone (CRH) from the hypothalamus stimulates adrenocorticotropin (ACTH) release from the pituitary corticotropes, derived from proteolytic processing of the precursor proopiomelanocortin. ACTH stimulates the zona fasciculata cells to produce cortisol, and also drives dehydroepiandrosterone sulfate (DHEAS) production from zona reticularis cells. Cortisol, but not DHEAS, exerts negative feedback on CRH and ACTH. Cortisol can bind to and activate the mineralocorticoid and glucocorticoid receptors (MR, GR), and various metabolic pathways lead to cortisol inactivation. In contrast, DHEAS is not itself an AR agonist, but DHEAS and DHEA metabolism to active androgens T and/or DHT occurs in peripheral and target tissues.

Based on these paradigms, drugs and hormones can be employed to "trick" these axes by inducing negative feedback and suppressing endogenous hormone production [16] (Fig. 1). For example, exogenous androgen administration will suppress GnRH and LH pulsations, impair testicular T synthesis, and lead to testicular atrophy—but the androgen itself would stimulate prostate cancer growth. Instead, estrogens or progestin accomplish GnRH and LH suppression without AR activation, and long-acting GnRH agonists desensitize the gonadotropes to block LH synthesis. GnRH agonists and now the antagonist degarelix have gained favor mainly due to lack of side effects specific for estrogens and progestins, including prominent gynecomastia and increased thromboembolism risk. Similarly, potent synthetic GR agonists like dexamethasone and prednisone will suppress CRH and ACTH release, which lowers production of not only cortisol but also DHEAS and other 19-carbon androgen precursors derived from the zona reticularis of the adrenal. To completely suppress adrenal-derived androgen production, however, doses must exceed physiologic glucocorticoid replacement, which causes iatrogenic Cushing syndrome with weight gain, osteoporosis, bruising, and glucose intolerance.

3. Enzymes and pathways

The Leydig cells of the testis and steroidogenic cells of the adrenal cortex possess the enzymatic machinery to convert cholesterol to pregnenolone and then to specific steroid products via specific pathways, which reflect the abundance and activities of these requisite enzymes. These cells represent one extreme of steroid metabolism: the efficient synthesis of one steroid with minimal side-products or subsequent catabolism of the target molecule. These enzymes and pathways have been reviewed in detail elsewhere [17], and here we will only review androgen biosynthesis.

The conversion of cholesterol to pregnenolone is catalyzed by CYP11A1 (cholesterol side-chain cleavage enzyme, P450scc). CYP11A1 is a mitochondrial or "type I" cytochrome P450 enzyme, which receives electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH) relayed via the membrane-bound flavoprotein ferredoxin reductase and then the soluble iron–sulfur protein ferredoxin in the mitochondrial matrix. Three equivalents of NADPH and molecular oxygen are consumed in converting cholesterol to pregnenolone in three discrete oxygenation steps. Cholesterol from the outer mitochondrial membrane is transferred to the inner mitochondrial membrane where CYP11A1 and ferredoxin reductase reside under the action of the steroidogenic acute regulatory protein (StAR) [18]. Although StAR's mechanism of action is not fully understood, the X-ray crystal structure of MLN64, which contains a StAR-like domain, contains a pocket, which binds one cholesterol molecule [19]. Although the MLN64 structure suggests that StAR physically transports cholesterol, other evidence suggests that StAR acts on the outer mitochondrial membrane [20], and StAR phosphorylation is essential for cholesterol transfer

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