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## Hormone whodunit: clues for solving the case of intratumor androgen production.

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## CCR Translations

See related article by Fankhauser et al., p. 5547

**Hormone Whodunit: Clues for Solving the Case of Intratumor Androgen Production**Karen E. Knudsen<sup>1,2,3,4</sup>

One of the key mechanisms by which prostate cancer cells evade hormone therapy is through intratumor testosterone production. New evidence points toward androstenedione as a potential precursor of intratumor androgen production and furthers nomination of AKR1C3 as a therapeutic target in advanced disease. *Clin Cancer Res*; 20(21); 5343–5. ©2014 AACR.

In this issue of *Clinical Cancer Research*, a study by Fankhauser and colleagues (1) yields insight into the mechanisms driving intratumor androgen. It has been more than half a century since the pioneering work of Charles Huggins and colleagues identified steroid hormone signaling as critical for prostate cancer growth and survival, yet the struggle persists to thwart this process and develop definitive management for advanced prostate cancer. Patients diagnosed with truly organ-confined disease have high expectation at cure, largely as achieved through surgical resection and/or radiotherapy. However, durable treatment for patients with non-organ-confined prostate cancer presents a formidable clinical challenge (2). The first line of therapeutic intervention for this stage of disease is androgen-deprivation therapy (ADT), which entails the use of pharmacologic agents that suppress testicular androgen synthesis. Such therapeutic regimens are intended to deprive the androgen receptor (AR) of the ligand required for activation of this ligand-dependent transcription factor, testosterone or the more potent reduced form dihydrotestosterone (DHT). ADT is effective at suppressing testicular androgen synthesis, and biochemical validation is manifest through a measurable decline in prostate-specific antigen (PSA), a protein secreted into the serum and encoded by a gene whose activation is stringently dependent on AR function. To further suppress AR activity, ADT is frequently used in combination with direct AR antagonists that compete with androgens for binding to the AR and prevent the receptor from engaging in transcriptional activation. Notably, the vast majority of patients given ADT and/or ADT in

combination with AR antagonists, benefit from both PSA decline and marked tumor regression. Such dramatic and reliable responses strongly support the contention that advanced prostate cancer is exquisitely dependent on AR function for growth and survival (3). Unfortunately, ADT-induced remission is transient, and patients relapse within a median time of 2 to 3 years. Disease recurrence is heralded by a rising PSA, indicating that the therapeutic regimens are no longer suppressing AR activity, followed by radiographic evidence of recurrent tumor formation. It is this stage of disease, called castrate-resistant prostate cancer (CRPC), for which there is no durable cure, thus underscoring the need to determine how to more effectively suppress AR activity and achieve sustainable disease management.

Strikingly, the field has witnessed remarkable gains over the last several years with regard to molecular understanding of recurrent AR activity and CRPC progression (4). It is now clear that tumors "rewire" AR signaling in response to ADT through multiple mechanisms that restore receptor function in a low hormone environment (5). These mechanisms are not mutually exclusive, and include AR amplification, somatic mutation of AR that facilitates utilization of alternative ligands, generation of truncated AR that is constitutively active and lacks a ligand-binding domain, and most intriguingly, androgen production from within the tumor itself. The hypothesis that intratumor androgen production occurs emerged from the surprising observation that in CRPC, induction of pathways that convert weak adrenal androgens to testosterone and DHT occurs with significant frequency (6–11). The importance of this biochemical observation fast-tracked the concept that CYP17A1, an enzyme key to androgen production in the adrenal gland and in tumor tissue, could be effectively targeted in CRPC. This concept bore fruit in the clinical setting through the approval of abiraterone acetate as a treatment for patients with CRPC (12). FDA approval was obtained in part based on a study of 1,195 patients, for which overall survival improved to 15.8 months (abiraterone arm) from 11.2 months (placebo). Although abiraterone acetate has not yet led to cure, these results energized a field that had not seen introduction of new, effective anti-CRPC agents in decades. Given this success, the pressure is

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now on to sleuth out the molecular mechanisms that underlie intratumor androgen synthesis and develop of novel means to suppress this process.

To date, three prevailing hypotheses exist to explain how it is that the patient can be castrate (with regard to serum testosterone levels) yet androgen levels could be high within the tumor itself (6–11). First, it is proposed that testosterone is produced in the tumor through CYP17A1-dependent conversion of adrenal androgens to testosterone. Within the tumor itself, it is known that testosterone can be converted to DHT through the action of 5 $\alpha$ -reductase, a resident enzyme. Through these means, it is hypothesized that testosterone and/or DHT levels rise to levels sufficient for AR activation and resultant tumor growth/progression. A second, "backdoor pathway" proposes that pregnane (progesterone or 17OH-progesterone) is 5 $\alpha$ -reduced, ultimately resulting in DHT production and circumventing testosterone as an intermediate. Finally, the "*de novo*" model proposes that androgens in the tumor can be directly generated from cholesterol, resulting in DHT production, and that could bypass the androstenedione–testosterone pathway. The 5 $\alpha$ -dione (5 $\alpha$ -dione) pathway can also

circumvent testosterone, and it differs from the backdoor pathway in that it begins with adrenal precursors instead of cholesterol. Given the importance of targeting this process in the clinical setting, developing a more robust understanding of which pathway(s) predominate in CRPC is a translational priority.

In the study by Fankhauser and colleagues (1), biochemical analysis of human tissue of multiple stages gives indication that reduction of androstenedione may be a significant source of androgen production in CRPC. Using tissue samples obtained from transurethral resection or radical prostatectomy, *ex vivo* challenge was performed using precursors of testosterone, cholesterol, progesterone, androstenedione, DHEA, or control. After a 4-day incubation period, hormone extraction and identification studies were performed. At this time point, only androstenedione challenge resulted in significant testosterone production (Fig. 1). A notable aspect of this finding is the ability of exogenous androstenedione to result in testosterone production even in nonneoplastic tissue (derived from benign prostatic hyperplasia), and surprisingly, that the levels of production in this benign disease exceeded that observed in

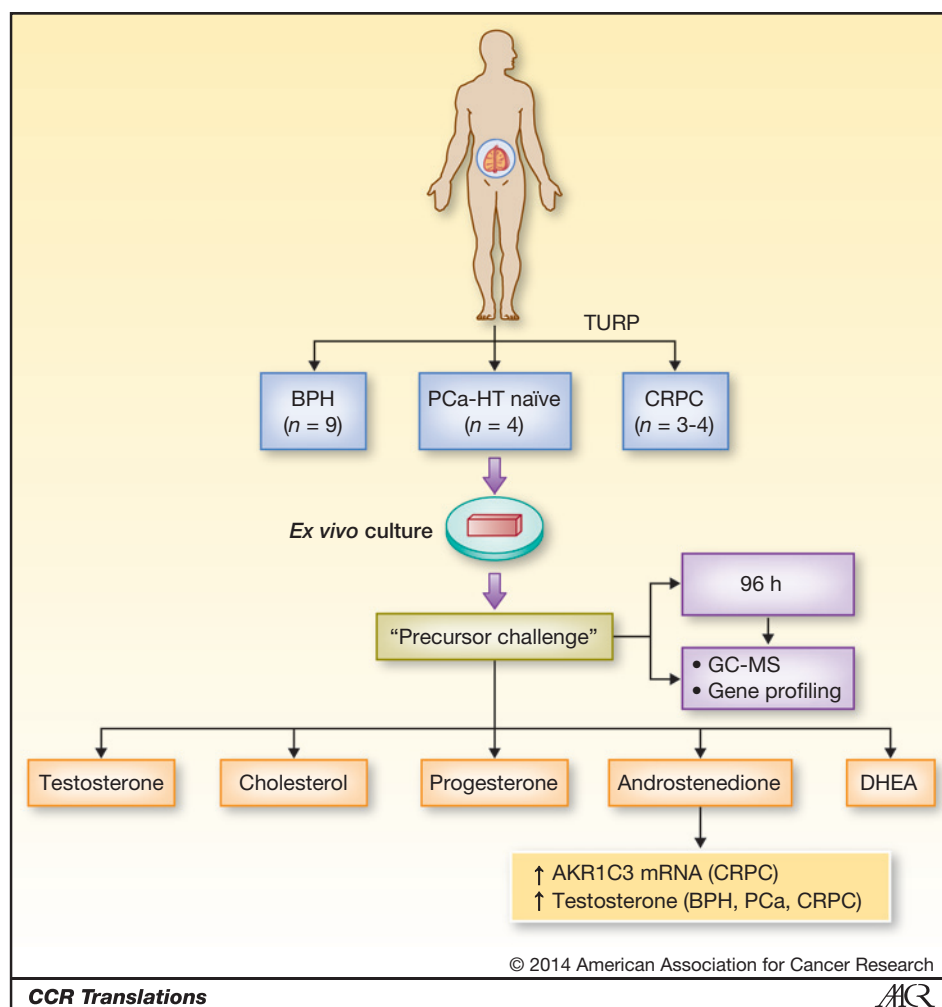


Figure 1. Precursor challenge studies in *ex vivo* analyses implicate androstenedione as a significant source of androgen production in CRPC. BPH, benign prostatic hyperplasia; PCa-HT, prostate cancer hormone therapy; TURP, transurethral resection.

hormone therapy-naïve prostate cancer. The highest levels of testosterone production were observed in CRPC, but the ultimate fate of testosterone production did not appear to be reduction to DHT; rather, generation of androsterone was observed. In parallel, a gene signature of enhanced HSD17B isoenzyme activity and upregulation of HSD17B5/AKR1C3 (an aldo-keto reductase that catalyzes reduction of androgen precursors to testosterone) were found in the CRPC specimens, consistent with the concept of androstenedione conversion to testosterone.

Combined, these observations point toward androstenedione as a potential precursor of intratumor androgen production and provide further evidence supporting development of AKR1C3 as a therapeutic target in advanced prostate cancer. Indeed, previous studies identified AKR1C3 upregulation as a frequently occurring event in CRPC, and efforts to develop selective AKR1C3 inhibitors are already under way (13). Despite these translational gains, some questions remain that will be essential to address. First, it is remarkable that the capacity of exogenous androstenedione to result in testosterone production was conserved in benign tissue, and perhaps even more effective when compared with the capacity of this conversion pathway in hormone therapy-naïve tumors. If this is part of a "normal" biologic process, the relative impact of the pathway on tumor development and/or tumor progression will be critical to discern. Second, inclusion of an expansion cohort will be of certain importance; as access to these tissues is limited, the present study examined only four hormone therapy-naïve and three to four CRPC specimens (dependent on the endpoint) and without replicates. Moreover,

the single time point of 4 days after challenge may miss the window of detection for intermediates, and further inclusion of methods to assess 5 $\alpha$ -dione will likely be important. Thus, engagement of other pathways cannot be ruled out, and whether the *ex vivo* culture allows for faithful recapitulation of the *in vivo* androgen production pathway should be considered. Third, although androstenedione-mediated testosterone production was apparent, less clear is whether the levels achieved resulted in biologically relevant upregulation or AR activity, as this endpoint was not monitored. The need to include such assessments in future studies is underscored by the surprising observation that reduction to the more potent AR ligand, DHT, was not well observed in the *ex vivo* studies.

In sum, the study by Fankhauser and colleagues (1) provides an exciting step toward the "hormone whodunit" identification of pathway(s) responsible for intratumor androgen production, restored AR activity in the presence of ADT, and development of lethal prostate cancers. Moreover, the study furthers nomination of AKR1C3 as a therapeutic target in advanced disease.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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