Hormone Whodunit: Clues for Solving the Case of Intratumor Androgen Production

Karen E. Knudsen

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.
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 5a-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 5alpha-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 5alpha-dione (5α-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, androstedione, 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...
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 isozyme activity and upregulation of HSD17B5/ARK1C3 (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 ARK1C3 as a therapeutic target in advanced prostate cancer. Indeed, previous studies identified ARK1C3 upregulation as a frequently occurring event in CRPC, and efforts to develop selective ARK1C3 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 5α-dione will likely be important. Thus, engagement of other pathways cannot be ruled out, and whether the in 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 ARK1C3 as a therapeutic target in advanced disease.

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References
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