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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

More evidence intratumoral DHT synthesis drives castration-resistant prostate cancer

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A gain-of-function stabilizing somatic mutation in 3β-hydroxysteroid dehydrogenase type 1 (3βHSD1, HSD3B1) was reported in castration-resistant prostate cancer. The A→C nucleotide polymorphism replaced asparagine-367 with threonine (3βHSD1-N367T) as a homozygous somatic mutation in a subset of castration-resistant prostate cancers by loss of heterozygosity of the wild-type allele. Increased stability of 3βHSD1-N367T was associated with decreased ubiquitin-mediated degradation and higher levels of dihydrotestosterone (DHT). The studies suggest that genetic instability in castration-resistant prostate cancer favors the more stable 3βHSD1-N367T mutant that contributes to drug resistance. A somatic mutation in a steroid metabolic enzyme required for DHT synthesis provides further support for intratumoral androgen synthesis contributing to prostate cancer progression.

It has been known for >60 years that growth of prostate cancer depends on testicular androgen. Prostate cancers undergo remission for 1–2 years following androgen deprivation therapy, but recur in the absence of testicular androgen. Recurrence of prostate cancer growth during androgen deprivation therapy by medical castration using luteinizing hormone releasing hormone (LHRH) agonists has been attributed to increased expression of the androgen receptor (AR) and its coregulators, and to intratumoral androgen biosynthesis.[1-5] Synthesis of DHT, the most potent androgen that activates AR transcriptional activity, depends on a series of metabolic enzymes that catalyze the oxidation and reduction of steroid precursors from the adrenal gland or from cholesterol.

A recent study by Chang *et al.*[6] provides evidence that a gain-of-function 3βHSD1 somatic mutation contributes to prostate cancer progression by conferring resistance to proteasome-mediated degradation. 3βHSD1, like its other family member 3βHSD2, is an intracellular membrane-bound steroid metabolic enzyme with dual functions: Oxidization of the 3β-hydroxyl to 3-keto of 5α-configured steroids, and isomerization of the Δ5 carbon-carbon double bond to Δ4. 3βHSD1 and 3βHSD2 utilize NAD+ cofactors to catalyze four irreversible oxidative hydroxysteroid reactions in the pathway toward DHT synthesis: Conversion of pregnenolone to progesterone, conversion of 17α-hydroxypregnenolone to 17α-hydroxyprogesterone, conversion of dehydroepiandrosterone (DHEA) to Δ4-androstenedione, and conversion of Δ5-androstenediol to testosterone.

Both 3βHSDs are essential enzymes in the *de novo* synthesis of DHT. 3βHSD1 contributes to androgen metabolism primarily in peripheral tissues such as prostate, and 3βHSD2 is expressed predominantly in the adrenal gland and testis. One pathway of DHT synthesis that is independent of testosterone synthesis in castration-resistant prostate cancer is the conversion of adrenal-derived DHEA by 3βHSD1 to Δ4-androstenedione, which is converted by 5α-reductase to 5α-androstanedione, and then by 17β-HSD to form DHT.[7] The gain-of-function 3βHSD1-N367T mutant described by Chang *et al.* extends the half-life of 3βHSD1 and is associated with increased synthesis of DHT from DHEA. The studies suggest that a somatic mutation in a steroid metabolic enzyme contributes to prostate cancer progression.

Rare loss or gain-of-function mutations can significantly impact reproductive function and provide insight into basic mechanisms. Loss-of-function AR germline mutations that cause the androgen insensitivity syndrome and a female external phenotype in affected genetic males demonstrate the requirement for AR in male reproductive system development. Loss-of-function 5α-reductase mutations cause an androgen insensitivity phenotype at birth and demonstrate a requirement for DHT in male reproductive development. Gain-of-function AR somatic mutations in prostate cancer can expand the repertoire of steroids that activate AR. Loss-of-function 3βHSD2 mutations cause incomplete masculinization in the male and a form of congenital adrenal hyperplasia, which in the female fetus can result in partial virilization due to the accumulation of adrenal androgen. The lack of reported loss-of-function 3βHSD1 mutations may reflect the requirement for placental synthesis of progesterone during pregnancy.[8] The 3βHSD1 gain-of-function gene mutation described by Chang *et al.* provides additional evidence that intratumoral DHT synthesis contributes to the growth of castration-resistant prostate cancer.

In humans, high circulating levels of the adrenal androgen DHEA-sulfate are taken up by prostate cancer cells and converted to DHEA, a substrate for 3βHSD1 in the synthesis of DHT. Metabolism of DHEA, 5α-androstane-3α,17β-diol or other adrenal precursors to testosterone or DHT is required for the activation of wild-type AR.[9] However, rare somatic AR mutations in prostate cancer can introduce structural stability in the ligand-binding domain that facilitates direct activation of the AR mutant by DHEA.[10,11] Such gain-of-function AR

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mutations emphasize the importance of AR mediated gene transcription in prostate cancer growth and progression. A role of 3βHSD1 in intratumoral DHT synthesis from adrenal precursors suggested by the gain-of-function mutation described by Chang *et al*. supports the contribution of intratumoral androgen production to prostate cancer growth during androgen deprivation therapy.

However, an array of therapeutic interventions that target AR or androgen biosynthetic enzymes has thus far met with only limited success in blocking the growth of castration-resistant prostate cancer. AR remains a principal target of moderate affinity antiandrogens that compete with high affinity intratumoral DHT. The effectiveness of antiandrogen therapy in early stage prostate cancer demonstrates the contribution of AR to prostate cancer growth. However, antiandrogen treatment of most cases of late stage castration-resistant prostate cancer extends life by only several months. Even though AR remains a critical target in the growth of advanced prostate cancer, genetic instability inherent to cancer cells enables them to circumvent drug intervention by optimizing AR activation through multiple mechanisms. This includes rare cases of gain-of-function mutations in AR and most recently 3βHSD1.

Intratumoral DHT derived from adrenal precursors, *de novo* synthesis from cholesterol, or backdoor pathways independent of testosterone synthesis,[9,12] contributes to AR activation and prostate cancer growth. The multiple metabolic pathways involved in DHT synthesis provide a growing list of potential targets for pharmacological intervention. Abiraterone acetate slows prostate cancer growth through the inhibition of cytochrome P450 17A1 (CYP17A1), an enzyme that converts progesterone precursors to DHT,[13] and by weak inhibition of 3βHSD1.[14] Studies of Chang *et al*. suggest that loss of response to abiraterone acetate may reflect in part genetic selection of the more stable 3βHSD1-N367T allele, and therefore provide evidence for the contribution of genetic instability to castration-resistant tumor growth. Expression of wild-type or mutant 3βHSD1 is heterogeneous among prostate cancer cell lines and tumors,[6] with low 3βHSD1 protein levels in LAPC-4 cells, low 3βHSD1 mRNA in locally confined prostate cancers,[15] higher 3βHSD1 protein in LNCaP cells, and higher 3βHSD1 mRNA in castration-resistant prostate cancer.[4] Therapy to block 3βHSD1 activity and inhibit the synthesis of DHT from DHEA supports the importance of intratumoral DHT synthesis to prostate cancer growth, and further highlights the complication of genetic adaptability to treatment outcome. A multi-targeted approach to inhibit AR and key steroidogenic enzymes earlier in the course of disease progression may provide the best chance for reduced mortality from prostate cancer.

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