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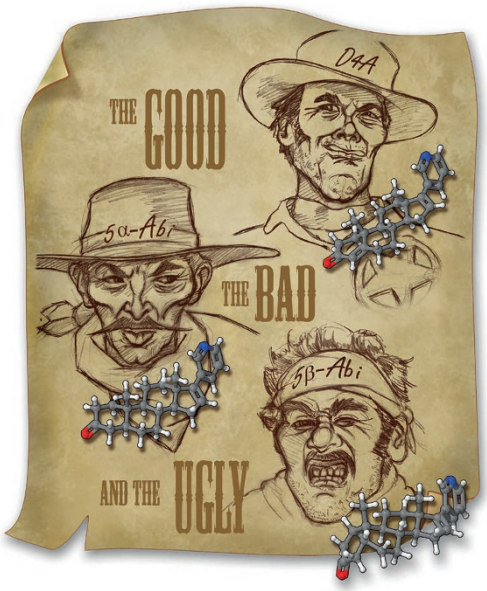
PROSTATE CANCER

Interfering with abiraterone metabolism to optimize therapy



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New research into the metabolic pathways of abiraterone and its metabolite Δ4-abiraterone (D4A) reveals steroid 5α-reductase as a target to improve the effectiveness of abiraterone treatment in patients with castration-resistant prostate cancer (CRPC). Addition of the 5α-reductase inhibitor dutasteride to treatment with abiraterone increases serum levels of therapeutic D4A and reduces the levels of downstream 5α-reduced metabolites that promote prostate cancer progression.

The androgen synthesis inhibitor abiraterone that blocks 17α-hydroxylase/17,20-lyase (CYP17A1) is a widely used medication for men with CRPC, resulting in decreased levels of testosterone and dihydrotetosterone, reducing androgen receptor (AR)-driven tumour progression. In the past year, Nima Sharifi and colleagues, the authors of the new study published in *Nature*, had found that abiraterone is converted into the metabolite D4A, which has increased antitumour potency compared with its parent compound. However, whether other metabolites with clinically relevant activity exist remained unclear.

"D4A has structural features identical to testosterone, so we thought it might also be metabolized by 5α-reductase," Sharifi told *Nature Reviews Urology*. Using three prostate cancer cell lines, the team found that D4A is irreversibly reduced to 3-keto-5α-abiraterone by 5α-reductase or to 3-keto-5β-abiraterone by 5β-reductase, which in turn can be reversibly reduced into their respective 3α-OH or 3β-OH congeners. The same six, previously undescribed, metabolites were also found in an analysis of serum samples from 12 men undergoing abiraterone treatment.

5β-reduction changes the conformation of the steroid structure resulting in inactive compounds; hence, the researchers focussed their subsequent investigations on the 5α-reduced D4A metabolites, first assessing their activity. In cell culture experiments, 5α-reduction of D4A resulted in markedly reduced inhibition of D4A target enzymes, such as CYP17A1. Notably, 3-keto-5α-abiraterone, and to a reduced extent its 3α-OH congener, induced expression of androgen-responsive genes, such as *KLK3*, which encodes PSA. The team then tested AR-stimulating effects of 3-keto-5α-abiraterone in CRPC xenograft models *in vivo* and found significantly shorter progression-free survival ($P<0.01$) compared with vehicle-treated mice, demonstrating that this metabolite has tumour-promoting activity, in contrast to its parent compounds abiraterone and D4A. Furthermore, prolonged (6-month) treatment of cell lines with abiraterone or D4A resulted in increased expression of 5α-reductase, resulting in increased conversion of D4A into the tumour-promoting 3-keto-5α-abiraterone.

Dutasteride is a 5α-reductase inhibitor that is used in the treatment of benign prostatic hyperplasia and is currently being investigated in a clinical trial for its use in the treatment of patients with CRPC. The team analysed serum samples from 16 men enrolled in this trial before and after addition of dutasteride to abiraterone treatment and found that dutasteride use resulted in an 89% decline in 3-keto-5α-abiraterone concentration ($P<0.001$) and around twofold increase in D4A concentration ($P=0.002$). "Manipulation of abiraterone metabolism is specifically and clinically achievable to optimize antiandrogen therapy in prostate cancer," summarizes Sharifi. "Plans are in discussion to perform a dedicated clinical trial to determine the clinical efficacy of fine-tuning abiraterone metabolism."

Clemens Thoma

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