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PROSTATE CANCER

The pathway to progression: DHT biosynthesis

New data, published in *Clinical Cancer Research*, provide evidence that the transition of primary prostate cancer to castration-resistant disease could coincide with a switch in the preferred metabolic pathway of dihydrotestosterone (DHT) biosynthesis in tumour tissue. This observation increases our understanding of progression to castration resistance and could help in the discovery of new therapies for this disease.

Previous results had indicated that adrenal-derived androstenedione is the preferred substrate of 5α-reductase for DHT biosynthesis in castration-resistant prostate cancer (CRPC), bypassing the requirement for testosterone as a DHT precursor. Using a novel mixed-substrate approach in this study, Dai and colleagues investigated the metabolic pathway of adrenal-derived DHT biosynthesis in primary prostate cancer.

Prostate tissue from 17 men undergoing radical prostatectomy for clinically localized disease were cultured *ex vivo* in media containing equimolar concentrations of radiolabelled androstenedione and unlabelled testosterone, to enable the identification of the enzymatic conversion of each substrate.

Within 48 h the majority of both substrates were converted into downstream metabolites; the principal metabolite of androstenedione was 5α-dione, whereas testosterone was primarily converted into DHT or, to a lesser degree, androstenedione. DHT arising from androstenedione was detected at the 7 h time point and was more abundant than DHT derived from testosterone over the course of the experiment. Notably, results derived from tissue samples from three patients receiving an oral 5α-reductase inhibitor therapy showed that this therapy blocked both conversion pathways; however, the conversion of testosterone to DHT was completely blocked, but the conversion of androstenedione to 5α-dione was only reduced. Furthermore, conversion of testosterone to androstenedione was increased in these samples.

Direct comparison of the use of androstenedione and testosterone in CRPC and primary prostate tissue was undertaken *in vitro* and *in vivo* using cell lines and a xenograft model. Conversion of androstenedione to 5α-dione was more efficient in CRPC cells and the CRPC xenograft model than conversion of testosterone to DHT; however, results for RWPE-1 (an immortalized benign prostate epithelial cell line) were similar to the substrate preference observed in primary prostate tissue.

Analysis of the metabolic pathway preferred in primary prostate tissue revealed that the reduction of androstenedione was comparable to the testosterone reduction, with testosterone being the marginally preferred substrate. Furthermore, no competition for 5α-reductase between substrates was observed.

These data provide evidence that the biosynthesis of DHT could occur through the 5α-dione pathway, bypassing the requirement for testosterone as a precursor. Thus, two distinctly nonredundant metabolic pathways exist via which gonadal testosterone and adrenal dehydroepiandrosterone are converted to DHT, both requiring 5α-reductase, but using different substrates. The switch in substrate preference for DHT biosynthesis could occur during the transition of primary prostate cancer to CRPC.

Increased understanding of steroidogenic pathways in prostate cancer could result in new androgen-directed therapies for this disease.

Louise Stone

> “the principle metabolite of androstenedione was 5α-dione, whereas testosterone was primarily converted into DHT”

ORIGINAL ARTICLE Dai, C. *et al.* Direct metabolic interrogation of dihydrotestosterone biosynthesis from adrenal precursors in primary prostatectomy tissues . *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-17-1313 (2017)