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PROSTATE CANCER

Steroid enzyme mutated in CRPC

A gain-of-function mutation in the steroid-synthesizing enzyme 3β-hydroxysteroid dehydrogenase type 1 (3βHSD1) has been identified in castration-resistant prostate cancer (CRPC), providing a possible mechanistic explanation for the accumulation of dihydrotestosterone (DHT) observed in CRPC tumours. "The occurrence of increased DHT concentrations in CRPC has been known for over 30 years but this is the first known missense change in the steroidogenic machinery that can explain this observation," says Nima Sharifi, who led this new research, published in the 29 August issue of *Cell*.

New generation treatment options for CRPC, such as abiraterone acetate, were designed to exploit the upregulation of DHT observed in these tumours. Abiraterone inhibits 17α-hydroxylase/17,20-lyase (CYP17A1), an enzyme that catalyzes the formation of dehydroepiandrosterone (DHEA), a key precursor of DHT. Thus, abiraterone exerts its effects by depriving the tumour of this steroid precursor and reducing downstream androgen signalling. The focus of this new research, 3βHSD1, catalyses another reaction in the androgen synthesis pathway—conversion of DHEA to androstenedione, the initial rate-limiting step in the synthesis of DHT from DHEA.

The multidisciplinary team of researchers led by Sharifi found that CRPC sometimes expresses a mutated form of 3βHSD1, referred to 3βHSD1(367T), which is characterized by a single nucleotide polymorphism that results in exchange of an asparagine residue for threonine at amino acid position 367. Investigators assessed the presence of wild type 3βHSD1 versus 3βHSD1(367T) in a number of CRPC cell lines and found that the mutated version was associated with increased flux of DHEA to DHT, suggesting that the mutation caused a gain of function. Subsequently, they demonstrated that 3βHSD1(367T) is resistant to ubiquitination and degradation, exhibiting a much longer half life (27 h) than the wild type protein (2.1 h), and confirmed the accelerated flux from DHEA to DHT in a mouse xenograft model. "Once we identified the missense change that is responsible for increased enzymatic activity, we knew this might explain clinical resistance to androgen deprivation therapy," explains Sharifi.

The allele responsible for 3βHSD1(367T) occurs at a frequency of 22% in the human germline, and although this might lead to homozygous inheritance in some cases, the researchers felt that it was more likely that the mutation arises as a result of heterozygous inheritance followed by loss of heterozygosity of the wild type allele or the acquisition of somatic mutations. Indeed, genomic DNA analysis of 40 men with CRPC revealed that 25 men were homozygous for the wild type allele, 11 men were heterozygous and only 4 men were homozygous for the mutant allele. Tumour DNA analysis, on the other hand, showed that 27% of the men who were heterozygous for the mutation exhibited loss of heterozygosity in their CRPC tumour. Moreover, 12% of the men with homozygous wild type inheritance had acquired the mutant allele in their cancer.

At this point, Sharifi and colleagues switched to a mouse model and made their most noteworthy finding—that genetic selection occurs for this gain-of-function mutation in response to abiraterone treatment. Xenograft tumours of LAPC4 cells (which do not harbour the mutation) were grown in orchiectomized mice and treated with either abiraterone ($n=8$) or vehicle ($n=8$). DNA extracted from these tumours revealed that the mutation was now present in 2 of 8 tumours treated with abiraterone, compared with none of the tumours treated with vehicle, providing compelling evidence for somatic acquisition of the mutation.

"We believe that tumours that harbour the mutant enzyme depend on its activity and may be effectively treated with pharmacological 3βHSD1 inhibition," Sharifi told *Nature Reviews Urology*. "We are now working toward the development of pharmacological 3βHSD1 inhibitors and determining how detection of this mutation can be used as a biomarker."

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