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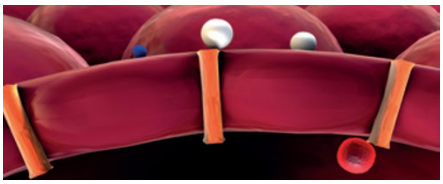
PROSTATE CANCER

SLCO2B1 variants correlate with castration resistance



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Substantial variations exist in the overall survival (OS) of patients with metastatic prostate cancer, and the development of resistance to androgen-deprivation therapy (ADT) often portends worse OS. Now, data from a genetic association study reveal that specific genetic variants of *SLCO2B1*, which encodes a dehydroepiandrosterone sulphate (DHEA-S) uptake transporter, are associated with significantly shorter OS in patients with metastatic prostate cancer.

The influence of three single-nucleotide polymorphisms (SNPs) — the exonic SNP rs12422149, and the intronic SNPs rs1789693 and rs1077858 — was examined in prostatectomy samples from a study cohort of 616 patients with metastatic prostate cancer who received ADT between 1996 and 2013. Patients whose prostatectomy samples were homozygous for the G form of rs1077858 were found to have significantly worse OS from the initiation of ADT, compared with those who were either heterozygous (GA) or homozygous for the A variant of this SNP (HR 1.35; 95% CI 1.07–1.71 for GG versus AA/GA forms of rs1077858).

In order to investigate the functional relevance of rs1077858, researchers then conducted *in vitro* investigations in 80 samples of normal prostate tissue derived from patients with prostate cancer. Samples that were homozygous for the G variant were found to have significantly higher SLCO2B1 expression than samples with other variants of *SLCO2B1*.

Taken together, these findings suggest that the functional consequences of homozygosity for the G form of rs1077858 are an increase in SLCO2B1 expression, resulting in increased DHEA-S uptake and, therefore, more rapid development of resistance to ADT. This suggested mechanism of action was confirmed by experiments in *SLCO2B1*-transfected LNCaP cells (a prostate cancer cell line), in which the level of SLCO2B1 expression was found to be positively correlated with DHEA-S uptake. Furthermore, *SLCO2B1* knockdown with siRNA in wild-type LNCaP cells resulted in a significant reduction in both SLCO2B1 expression and DHEA-S uptake.

These data indicate that increased uptake of testosterone precursors as a result of genetic variations in uptake transporters might explain some of the variations in time to progression to castration-resistant prostate cancer, which remains an important question in patients with this disease. The associations detected in this study also suggest that interventions targeting SLCO2B1 function in prostate cancer cells might delay the onset of castration resistance in patients with prostate cancer.

Peter Sidaway

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