

## **Increased transcriptional and metabolic capacity for lipid metabolism in the peripheral zone of the prostate may underpin its increased susceptibility to cancer.**

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The human prostate gland comprises three distinct anatomical glandular zones, namely the peripheral, central and transitional zones. Although prostate cancer can arise throughout the prostate, it is more frequent in the peripheral zone. In contrast, hyperplasia occurs most frequently in the transitional zone. In this paper, we test the hypothesis that peripheral and transitional zones have distinct metabolic adaptations that may underlie their different inherent predispositions to cancer and hyperplasia. In order to do this, we undertook RNA sequencing and high-throughput metabolic analyses of non-cancerous tissue from the peripheral and transitional zones of patients undergoing prostatectomy. Integrated analysis of RNAseq and metabolomic data revealed that transcription of genes involved in lipid biosynthesis is higher in the peripheral zone, which was mirrored by an increase in fatty acid metabolites, such as lysolipids. The peripheral zone also exhibited increased fatty acid catabolic activity and contained higher level of neurotransmitters. Such increased capacity for *de novo* lipogenesis and fatty acid oxidation, which is characteristic of prostate cancer, can potentially provide a permissive growth environment within the peripheral zone for cancer growth and also transmit a metabolic growth advantage to newly emerging clones themselves. This lipo-rich priming may explain the observed susceptibility of the peripheral zone to oncogenesis.

The authors declare no competing financial interests.

This work was supported by a Prostate Cancer Foundation Challenge Award and an Institute Strategic Programme Grant in Food & Health by the UK Biotechnology and Biological Sciences Research Council (BB/J004545/1). Next-generation sequencing and library construction was delivered via the BBSRC National Capability in Genomics (BB/J010375/1) at the Earlham Institute (Norwich, UK) by members of the Platforms and Pipelines Group.