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Differences in metabolism between androgen-dependent and castration resistant prostate cancer may lead to new therapies

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Advanced prostate cancer is usually treated by removing androgen, the male hormone that helps it grow. Although initially effective, this treatment often leads to the tumor becoming castration resistant- a lethal condition. Researchers from Baylor College of Medicine and University of Michigan, along with collaborators in other institutions, have determined that castration resistant prostate cancer (CRPC) has particular metabolic characteristics that may open new possibilities for treatment. The results appear in *Nature Communications*.

"Using an innovative approach to integrate gene expression and metabolomics data, we identified key metabolic pathways that are altered in prostate cancer," said corresponding author Dr. Arun Sreekumar, professor of Molecular and Cellular Biology, the Alkek Center for Molecular Discovery and the Verna and Marrs McLean department of Biochemistry and Molecular Biology at Baylor. "Of these metabolic pathways, the hexosamine biosynthetic pathway (HBP) showed significant alterations."

The researchers discovered that HBP is much less active in castrate resistant than in androgen-dependent prostate cancers. Furthermore, having reduced HBP activity is likely to enhance tumor growth.

"When we experimentally knocked down genes involved in HBP in cells similar to CRPC tumor cells, the cells responded with a marked increase

in proliferation, both in cell culture and animal experiments," said Sreekumar. "When the cells with reduced HBP received UDP-N-acetylglucosamine, a product of this metabolic pathway they lacked, the cells slowed down their growth."

When the researchers added UDP-N-acetylglucosamine and a clinically used anti-androgen (i.e., enzalutamide) to the CRPC cells growing in the laboratory, the cells reduced their proliferation further.

"This result is particularly noteworthy because our cells were essentially resistant to enzalutamide alone," said Sreekumar.

These results indicate that studying the metabolic characteristics of tumors resistant to therapy offers the possibility of discovering new targets to treat cancer. In this case, the results identify HBP as a potential therapeutic target for castration resistant prostate cancer, a disease that accounts for close to 30,000 deaths annually in the United States.

More information: Akash K. Kaushik et al, Inhibition of the hexosamine biosynthetic pathway promotes castration-resistant prostate cancer, *Nature Communications* (2016). DOI: 10.1038/ncomms11612

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