Researchers find new gene variant linked to deadly prostate cancer

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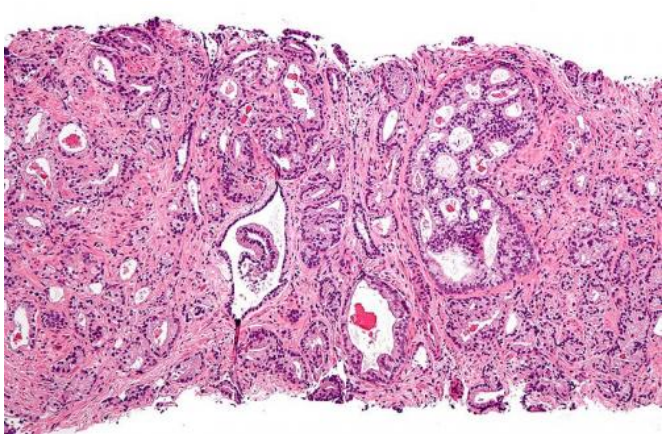

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia

Cleveland Clinic researchers have confirmed for the first time a mechanistic link between the gene HSD17B4 and deadly, treatment-resistant prostate cancer.

The research, led by Nima Sharifi, M.D., Cleveland Clinic Lerner Research Institute, Department of Cancer Biology, shows that men who lack a certain subtype of the gene may be more susceptible to aggressive prostate cancer that does not respond to treatment.

Dr. Sharifi and colleagues built upon their earlier seminal work in which they discovered that a gene called HSD3B1, when altered, enables prostate tumors to evade treatment and proliferate. They went on to show that the presence of this gene variant does in fact change treatment outcomes and overall survival in men.

In the current study published in the journal *Cell Reports*, Dr. Sharifi and his team studied a related gene, called HSD17B4. Previous research showed that HSD17B4 encodes enzymes that inactivate androgens (male hormones). Since androgens are essential for prostate cancer growth, inactivating them should prevent cancer advancement. But these enzymes have also been observed to be more abundant in advanced prostate cancer. Therefore, until now it remained unclear whether the enzymes promote or suppress prostate cancer.

Therapy for advanced prostate cancer—called androgen deprivation therapy (ADT), or chemical castration—blocks cells' supply of androgens, which they use as fuel to grow and spread. While ADT is successful early on, it eventually fails, allowing the cancer to progress to a lethal phase called castration-resistant prostate cancer (CRPC).

"We are hopeful that these findings will lead to more precise and effective treatments for prostate cancer," said Dr. Sharifi. "If men lack a specific isoform of this gene, we may be able to personalize their therapy."

To determine HSD17B4's role in the transition to CRPC, Dr. Sharifi's team analyzed its expression in tissue from patients with healthy prostates, localized prostate cancer and CRPC. They found that HSD17B4 expression levels were relatively the same in benign and local prostate cancer tissue, but significantly reduced in CRPC tissue, suggesting that HSD17B4 does play a role in preventing progression to CRPC.

Through a series of analyses, the researchers found that only one specific isoform of HSD17B4—isoform 2—enzymatically inactivated androgens and prevented tumor growth. It is expressed during the early phases of prostate cancer, but is lost, or suppressed, in CRPC (advanced prostate cancer). Isoforms vary in amino acid sequence and physiological function, but not DNA code.

The team also validated their findings in a

preclinical model. Their findings suggest that lack of isoform 2 leads to advanced CRPC. Additional research will be important to determine how HSD17B4 becomes silenced in CRPC and whether it may be used as a biomarker for patients at risk of dying from prostate cancer.

Hyun-Kyung Ko, Ph.D., Department of Cancer Biology, is first author on the study, which was supported by awards and grants from Howard Hughes Medical Institute, Prostate Cancer Foundation, American Cancer Society, and the National Cancer Institute.

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