Scientists discover new pathway to potential therapies for advanced prostate cancer

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UT Southwestern Medical Center researchers have narrowed the potential drug targets for advanced prostate cancer by demonstrating that late-stage tumors are driven by a different hormonal pathway than was thought previously.

While testosterone is generally known to stimulate the growth of the disease, advanced prostate cancer that is resistant to standard hormonal therapy actually is driven by a pathway that circumvents the male hormone, said Dr. Nima Sharifi, assistant professor of internal medicine and senior author of the study in Proceedings of the National Academy of Sciences.

"Our findings will change the framework for the way people think about this disease," said Dr. Sharifi, a researcher in UT Southwestern's Harold C. Simmons Comprehensive Cancer Center. "The general assumption is that the tumor accelerates through testosterone when, in fact, the pathway goes around it to the most potent hormone. We both found the existence of this pathway in models and patients, and have shown that these resistant tumors are clearly driven by this other pathway."

Prostate cancer is the most common cancer in men and trails only lung cancer as a leading cause of cancer death for men in the U.S. Some 220,000 men are diagnosed with the disease every year; 32,000 will develop the metastasized form – the focus of the current study – and will die from it.

In advanced prostate cancer cases, the testosterone driving the disease is converted into a more potent hormone that accelerates tumor growth. The standard treatment has been to deplete testosterone in the tumors, but they eventually become resistant to hormone depletion because they make their own androgens, or male hormones.

In the current study, UT Southwestern scientists analyzed prostate cancer cell lines, mouse models and fresh tumor tissue from patients. Their findings suggest that potential drug therapies need to target an enzyme responsible for initiating hormone production earlier in the process.

"This now suggests that a potential drug target is one step upstream in the pathway," said Dr. Sharifi. "This can be thought of as charting a map of the correct pathway. You have to figure out which way the river flows before you can block the river."

The findings also will help researchers develop accurate biomarkers of response and resistance to hormonal therapies, which eventually will help identify why and how prostate cancer tumors become resistant, he said.

Provided by UT Southwestern Medical Center