New target for prostate cancer resistant to anti-hormone therapies

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Arul Chinnaiyan, M.D., Ph.D. Credit: University of Michigan Health System

Prostate cancer becomes deadly when anti-hormone treatments stop working. Now a new study suggests a way to block the hormones at their

entrance.

Researchers from the University of Michigan Comprehensive Cancer Center have found that a protein called BET bromodomain protein 4 binds to the hormone androgen receptor downstream of where current therapies work – targeting androgen receptor signaling.

This could mean that when prostate cancer becomes resistant to current treatments, it might remain sensitive to a drug that targets BET bromodomain proteins. Results appear in *Nature*.

"We think we can target prostate cancer through androgen receptor signaling, rather than directly hitting the androgen receptor. These initial findings suggest the potential that a BET bromodomain inhibitor can work even when prostate cancer becomes resistant to anti-hormone therapies," says senior study author Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and S.P. Hicks Professor of Pathology at the University of Michigan Medical School.

The researchers used a compound called JQ1, designed to inhibit BET bromodomain proteins, to test the concept in cell lines and mice. They found that JQ1 blocked androgen signaling even when cells no longer responded to current anti-androgen therapies. The JQ1 BET bromodomain inhibitor blocked androgen receptor signaling, which is downstream of the androgen receptor, making it potentially unaffected by the acquired resistance related to hormone signaling.

The researchers also found that BET inhibitors appear to block several transcription factors, including the TMPRSS2-ERG gene fusion and MYC, known to drive prostate cancer.

Bromodomain inhibitors have been explored in blood cancers and a rare

cancer called NUT midline carcinoma. This is one of the first indications that BET bromodomain inhibitors may be beneficial in a common solid tumor.

A newly formed company, OncoFusion Therapeutics, co-founded by Chinnaiyan and study co-author Shaomeng Wang, Ph.D., will look at developing potential BET bromodomain inhibitors to attack prostate cancer.

"BET bromodomain represents one of the most exciting targets in epigenetics," Chinnaiyan says. "Developing new ways to treat castration-resistant prostate cancer is critical to improving survival for this disease."

More information: Paper: Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer, *Nature*, DOI: 10.1038/nature13229 , published online April 23, 2014

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