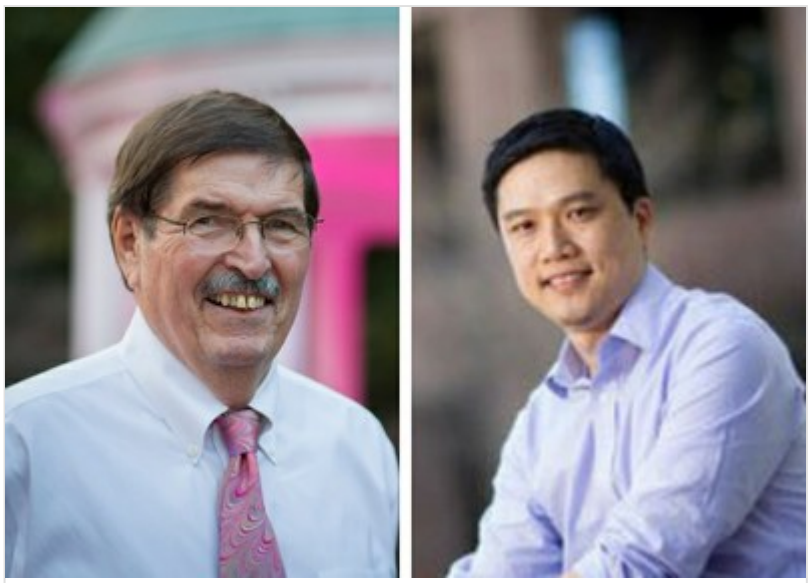
Insights about prostate cancer resistance could lead to treatment strategies

In the journal Molecular Cell, researchers led by UNC Lineberger's G. Greg Wang, PhD, and H. Shelton Earp, MD, describe the role of a protein variant called androgen receptor variant 7 (AR-V7), which is an alternative form of the androgen receptor that plays a key role in prostate cancer development and treatment.

October 5, 2018

Media Contact: Laura Oleniacz, 919-445-4219, laura_oleniacz@med.unc.edu



click to enlarge

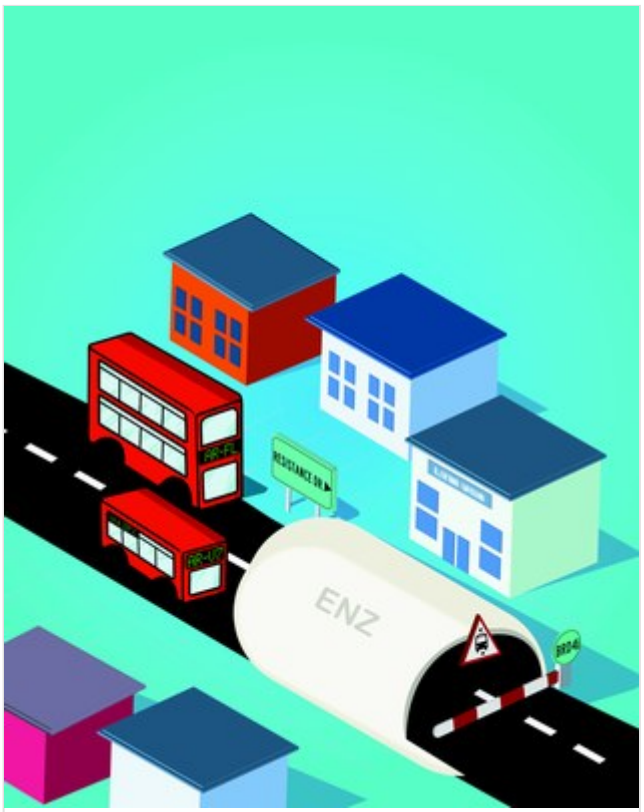
H. Shelton Earp, MD, and G. Greg Wang, PhD, have published a study that describe the role of androgen receptor variant 7 (AR-V7), an alternative form of the androgen receptor, that plays a key role in prostate cancer development.

Findings from a University of North Carolina Lineberger Comprehensive Cancer Center study could help predict which advanced prostate cancers will develop a key driver of resistance – a discovery that could lead to new therapeutic strategies.

In the journal **Molecular Cell**, researchers describe the role of a protein variant called androgen receptor variant 7 (AR-V7), which is an alternative form of the androgen receptor that plays a key role in prostate cancer development and treatment. While scientists have known about AR-V7 as a driver of resistance, the new study reveals previously unknown mechanisms of action for it.

“This is one of the unexposed transformation pathways that scientists have not understood before in prostate cancer,” said UNC Lineberger’s **G. Greg Wang, PhD**, associate professor in the UNC School of Medicine Department of Biochemistry &

Biophysics. “Prior to our study, scientists thought that AR-V7 binds to where the regular androgen receptor binds to in the cancer cell, but we found that’s not the case. We found that it goes to a new set of targets.”



click to enlarge

Credit: Yuva Oz. The drug enzalutamide (Enz) suppresses prostate cancer with the full-length androgen receptor, or AR-FL, but cancer cells with an alternative form of the receptor, AR-V7, are resistant.

The American Cancer Society estimates that 164,000 men will be diagnosed with prostate cancer in the United States this year, making it the most commonly diagnosed cancer in men, and more than 29,400 men are expected to die from the disease. More than 90 percent of prostate cancers are diagnosed at the local or regional stage, when they are highly treatable, which contributes to a five-year survival rate of nearly 100 percent. However, the 5-year survival for advanced disease is 30 percent.

Wang said the androgen receptor is a “master regulator” of prostate cancer. It is an intracellular receptor that’s triggered by signals from hormones like testosterone. It can then pass into the nucleus to act directly on the DNA to activate genes linked to cell growth. AR-V7 is created when the instructions for its DNA construction are spliced differently in a process known as “alternative splicing.”

The researchers found this receptor does not need to be bound to signals like testosterone to be active. Instead, it is always active. Furthermore, in addition to binding the same gene targets as the androgen receptor, they determined AR-V7 binds a new set of targets, working with a crucial protein partner called ZFX and other proteins.

“We’ve discovered an entirely different array of genes that this aberrantly spliced androgen receptor activates that the normal receptor does not; several of these may help trigger cancerous growth,” said UNC Lineberger Director **H. Shelton Earp, MD**, the Lineberger Professor of Cancer Research and a study co-author.

“These findings reveal a set of partner proteins and downstream targets that could potentially be druggable,” Wang said.

In cell studies in the laboratory, researchers used investigational compounds to try to block ZFX and another protein that works with AR-V7 in activating this new set of genes. They discovered this approach could suppress prostate cancer cell division.

Wang and Earp believe the study has dual implications: they used the findings to develop a gene signature associated with AR-V7 expression that could be used to identify patients that develop this mechanism of resistance, and the findings could lead to new therapeutic strategies.

“We have another set of potential targets to look at in castration-resistant prostate cancer, and we’re develop a gene signature that may help us indicate who’s going to develop this,” Earp said.

In addition to Earp and Wang, other authors include Ling Cai; Yi-Hsuan Tsai; Ping Wang; Yilin Zhao; Rui Lu; Young Whang; Deyou Zheng; Joel Parker; Dongxi Li; Huitao Fan; Jun Wang; Rohan Bareja; Andrew Sboner and Elizabeth M. Wilson.

The research was supported by the National Institute of Health, the Lineberger Professorship, a Kimmel Scholar Award, the V Foundation for Cancer Research V Scholar award, and a Concern Foundation for Cancer Research grant. Individual researchers were supported by the U.S. Department of Defense Prostate Cancer Research Program, a Lymphoma Research Foundation fellowship, the American Cancer Society and the Leukemia and Lymphoma Society.

Filed under: **Cancer Cell Biology**, **2018**