New target makes end run against therapy-resistant prostate cancer

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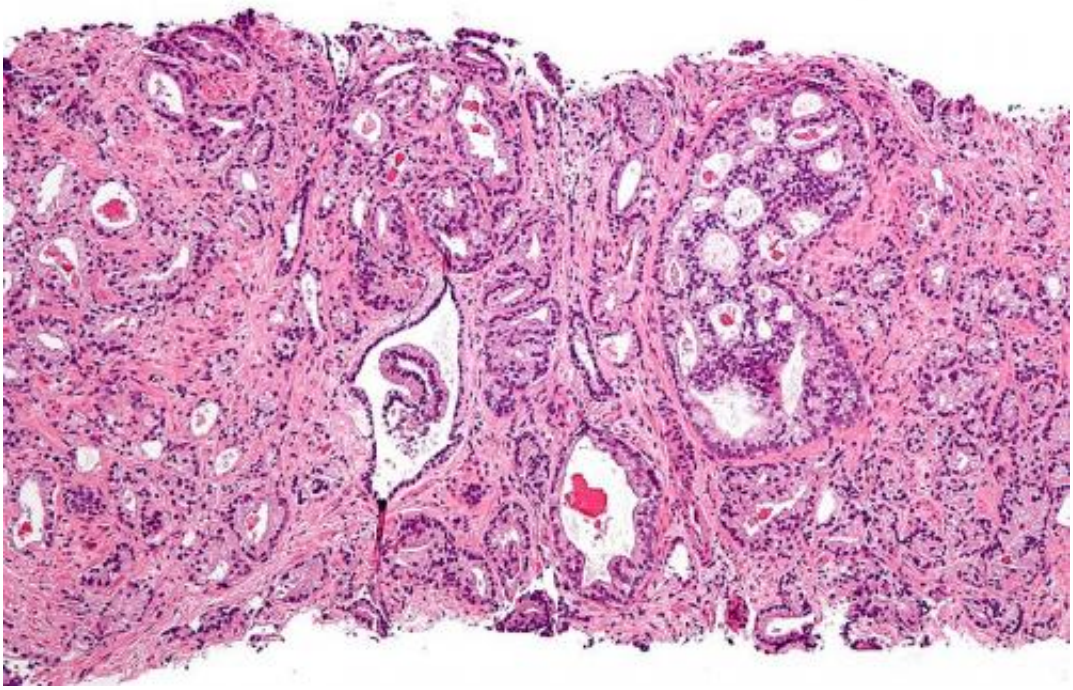

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

Researchers at UC Davis, in collaboration with the other institutions, have found that suppressing the nuclear receptor protein ROR-γ with small-molecule compounds can reduce androgen receptor (AR) levels in castration-resistant prostate cancer and stop tumor growth.

This novel approach does not directly target the AR, but rather inhibits

the gene that codes for the AR protein. Reducing AR levels could help patients overcome treatment-resistant prostate cancer and even rescue existing therapies. The research was published today in the prestigious journal *Nature Medicine*.

"This is a new target and a totally new way of hitting prostate cancer," said Hongwu Chen, a professor in the Department of Biochemistry and Molecular Medicine and lead author on the paper. "This strategy targets the root cause of the problem—the overexpression of the AR gene and its protein."

In the vast majority of prostate cancers, the AR gene becomes hyperactive, driving tumor growth and metastasis. Anti-androgen therapies can slow, and even stop, prostate cancer—for a time. But quite often the gene mutates to resist the treatment.

However, suppressing ROR-γ circumvents this resistance. Because the protein is required for AR gene expression, ROR-γ inhibition strongly reduces AR protein levels in tumor cells. By preventing AR protein synthesis, ROR-γ antagonists can potentially short-circuit the resistance process.

"Essentially all existing therapies work on blocking either activation of the AR or the genes it regulates," said Christopher P. Evans, professor and chairman of the Department of Urology and a co-author of the study. "However, as patients become resistant to existing agents, the AR becomes mutated, amplified and spliced. This (ROR-γ suppression) mechanism blocks the actual expression of the AR and its spliced forms."

To illuminate the relationship between ROR-γ and the AR gene, Chen's team studied a number of small molecule ROR-γ antagonists, both in cell lines and human tumors in mice. In each model, suppressing ROR-γ

reduced AR gene expression and AR protein levels, blocking tumor growth. These inhibitors showed broad effectiveness, inhibiting several AR variants, including AR-V7, which has been linked to resistance to advanced prostate cancer therapies enzalutamide and abiraterone.

"Blocking ROR-γ re-sensitizes castration-resistant prostate cancer to drugs that directly inhibit AR pathway signaling, such as enzalutamide," said Evans. "A combination approach can potentially be very effective."

In addition to reducing AR levels, ROR-γ suppression also can reduce the prevalence of several known oncogenes.

"ROR-γ suppression is quite remarkable," said the study's first author, Junjian Wang, a project scientist in the Department of Biochemistry and Molecular Medicine. "It can reduce levels of ERG and MYC, which are known to drive prostate cancer."

While ROR-γ was previously neglected in cancer research, it has been widely targeted for autoimmune diseases. As a result, there are a number of ROR-γ antagonists in the pipeline. These drugs could be retasked to fight prostate and possibly other cancers.

"ROR-γ has been extensively studied as a target for rheumatoid arthritis, inflammatory bowel disease, psoriasis and other autoimmune conditions," noted Chen. "Some of the drugs are orally available and have been found to be safe in early clinical trials. They could be a great help for patients with advanced prostate cancer."

More information: ROR-γ drives androgen receptor expression and represents a therapeutic target in castration-resistant prostate cancer, *Nature Medicine*, DOI: 10.1038/nm.4070

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