Prostate cancer: Androgen receptor activates different genes when bound to antiandrogens

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The androgen receptor in prostate cancer cells can activate different sets of genes depending on whether it binds with an androgen hormone or an antiandrogen drug, according to a new study led by researchers at The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC -

James).

The study found that when androgen receptor (AR) binds with testosterone or dihydrotestosterone, the activated receptor binds, as expected, to segments of DNA called androgen response elements.

But when the receptor binds with either of two antiandrogenic drugs, bicalutamide or enzalutamide, it then binds to different DNA sequences and activates entirely different sets of genes, including cancer-promoting oncogenes.

The researchers called these newly discovered AR binding sites on DNA "antiandrogen response elements" and showed that they activate genes that might enable tumor progression during antiandrogen treatment.

The findings, reported in *EMBO Journal*, suggest that the treatment of prostate cancer with antiandrogenic drugs should include agents that target antiandrogen-regulated oncogenes.

"The discovery of antiandrogen response elements was completely unexpected," says principal investigator and OSUCCC - James researcher Qianben Wang, PhD, associate professor of molecular virology, immunology and medical genetics.

He noted that antiandrogen agents are known to work by competing with androgens to bind to AR, thus inhibiting androgen-induced gene expression.

"But we found that antiandrogens can also trigger AR to bind to DNA sequences that are distinctly different from androgen response elements, and thus regulate genes relevant to prostate cancer development," Wang says.

Prostate cancer is the most frequently diagnosed cancer in men. An estimated 220,800 new cases are expected in the United States in 2015, along with 27,540 deaths from the disease.

In advanced hormone-dependent prostate cancer, hormone-activated androgen receptor drives tumor growth. Antiandrogen drugs such as bicalutamide and enzalutamide bind with androgen receptor to prevent them from activating genes that drive cancer progression.

Although initially responsive to these drugs, prostate cancer ultimately progresses to a lethal, treatment-resistant state that is currently incurable. "Our findings suggest that improved antiandrogen therapies could be achieved by simultaneously targeting antiandrogen-regulated oncogenes," Wang says.

Wang and first author Zhong Chen, a research scientist at the OSUCCC - James, developed most of the study's scientific concepts. They and their colleagues conducted the research using prostate cancer cell lines and samples of human prostate tumors and adjacent normal tissues.

Key findings include:

- The team precisely categorized androgen response elements into four distinct classes;
- Bicalutamide and enzalutamide enhanced the binding of AR to a group of genomic locations that lack androgen response elements;
- The oncogene CPEB4 showed a significant increase in expression in prostate cancer cells treated with enzalutamide compared with untreated and androgen-treated cells;
- Silencing CPEB4 enhanced the ability of enzalutamide to inhibit the proliferation of prostate cancer cells.

"Overall, we believe we've discovered a general mechanism for ligand-specific gene expression by certain ligand-dependent receptors," Wang says.

More information: *EMBO Journal*, onlinelibrary.wiley.com/doi/10 … j.201490306/abstract

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