Researchers Identify New Source of Drug Resistance in Prostate Cancer

A new study shines light on one cause of resistance to androgen receptor-targeting drugs.

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For designers of targeted drugs, the biggest bullseye in prostate cancer has been the androgen receptor — a specialized net on prostate cells that snares androgen molecules to spur the cells' growth. Drugs that block, or inhibit, the receptor can halt the cancer, but not all patients benefit from them, and nearly all those who do respond eventually become resistant.

Scientists have found that resistance often occurs because the androgen receptor (AR) regains the ability to switch on the cell's growth machinery even when the receptor is plugged with a drug molecule. But researchers also know that cancer cells usually harbor more than one backup plan: They have a variety of ways of circumventing a drug that initially worked well.

In a recent paper, Dana-Farber investigators uncovered one such mechanism: surplus production of a protein called CREB5. They found that advanced prostate cancers with an overactive CREB5 gene, or with too many copies of it, were able to proliferate after treatment with one of the newest AR inhibitors.

The discovery, published in Cell Reports, suggests that drugs targeting CREB5 could be effective in prostate cancers resistant to AR-blocking drugs. Although such drugs do not yet exist, they are under development.

"CREB5 has been shown to be overexpressed in some glioblastoma brain cancers and kidney cancers," said Dana-Farber's Justin Hwang, PhD, who led the study with William Hahn, MD, PhD, the Institute's chief scientific officer. "This suggests that targeting CREB5 could be useful in these malignancies as well as prostate cancer."

Flagging the CREB5 gene

Investigators first flagged the CREB5 gene as a potential culprit in AR inhibitor resistance in research beginning in 2015. Hahn's team screened 17,255 genes and examined more than 1,000 prostate tumor samples to see which genes were abnormally active and promoted resistance to the AR inhibitor enzalutamide. The standout gene — the one whose activity jumped highest in these samples — was CREB5.

In the new study, researchers conducted an array of tests to determine whether CREB5 does in fact drive an enzalutamide resistance pathway. In laboratory cell lines, animal models, and three-dimensional models of prostate tumors, the investigators found that overexpression of CREB5 led to resistance of all AR inhibitors tested, including enzalutamide.

“We found that over 25% of the clinical samples had very high levels of CREB5 activity,” Hwang said. The increase could be due to excess copies of the CREB5 gene at either the DNA or RNA level.

Hahn’s team found that when prostate cancer cells are treated with enzalutamide, CREB5 interacts with key genes to perk up the AR, increasing its output of cell growth signals.

CREB5 is a transcription factor — controlling how quickly genetic information is transferred from DNA to RNA — a class of proteins that is notoriously difficult to thwart with small molecule drugs. But, Hwang notes, it has a unique structure relative to other transcription factors and targeting this structure may interfere with its activity in cancer cells.

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