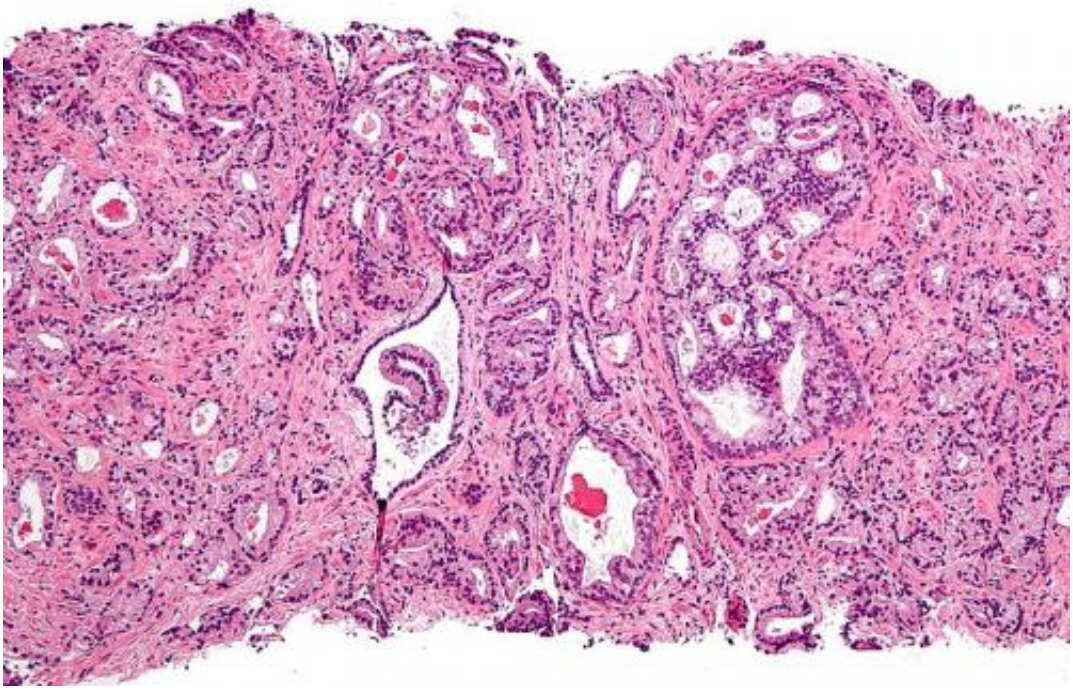
Scientists identify gene contributing to prostate cancer drug resistance

January 15 2019



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

Researchers have discovered how a gene involved in regulating hormone receptors may contribute to drug resistance in some prostate cancer patients.

Their findings, published in *eLife*, suggest that disrupting specific activity of the GREB1 gene could be explored for developing more

effective therapies in future.

Androgens, a male hormone, encourage the growth of prostate cancer cells. Hormone therapies (or 'antiandrogens') have been developed to counter this activity. These treatments, which target a protein molecule activated by the hormone—the androgen receptor (AR) - are effective against advanced prostate cancer but are hindered by a type of drug resistance called castration-resistant prostate cancer (CRPC). The most common cause of this resistance is an increase in both the amount and activity of AR.

Previous studies have shown that increases or mutations in AR are present in over 50% of CRPC patients, and that increases in AR are associated with greater resistance to the next-generation AR inhibitors: abiraterone and enzalutamide.

"Studies have also revealed several differences in AR activity in prostate cancer," explains first author Eugine Lee, Research Fellow in Charles Sawyers' lab at Memorial Sloan Kettering Cancer Center, US. "Notably, these differences occur in the absence of genetic alterations in AR, which are generally found only in CRPC. A possible explanation is that AR activity is encouraged by coactivators—other genes and proteins that help the function of AR—and we wanted to see if this is the case."

Lee and her team first isolated prostate cancer cells with low versus high AR activity. They found that those with high AR output have reduced sensitivity to enzalutamide, in the absence of changes in AR protein expression.

They next identified three genes that were most active in cells with high AR output: GREB1, KLF8 and GHRHR. "Of these genes, we prioritised GREB1 for further investigation because it has higher expression levels in primary prostate tumours with high AR activity," says Lee.

Their analysis showed that GREB1 increases AR activity through a novel two-part mechanism: it binds AR and promotes its activity by recruiting AR coactivators (enzymes such as EP300/CBP); and it improves the efficiency of AR binding to DNA, which further enhances AR activity. Importantly, the team found that inhibiting GREB1 converted cells with a high AR output to a low-output state, and improved the effectiveness of enzalutamide treatment.

"Collectively, our results implicate GREB1 as an amplifier of AR activity that contributes to prostate cancer progression and promotes antiandrogen resistance in disease models," concludes senior author and Howard Hughes Medical Institute Investigator Charles Sawyers, Chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center.

"For now, further research is needed to understand the clinical implications of this work—particularly whether GREB1 levels in CRPC patients can be used to predict their response to next-generation AR therapy."

More information: Eugine Lee et al, GREB1 amplifies androgen receptor output in human prostate cancer and contributes to antiandrogen resistance, *eLife* (2019). DOI: 10.7554/eLife.41913

Provided by eLife