Research helps explain why androgen-deprivation therapy doesn't work for many prostate cancers

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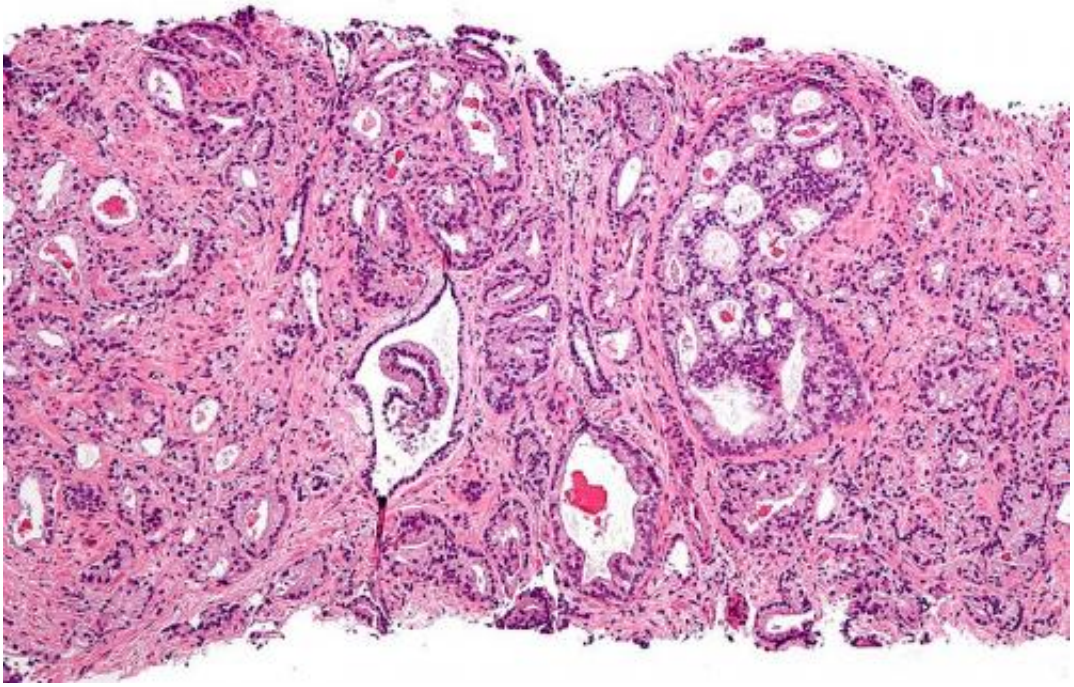

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

Metastatic prostate cancer, or prostate cancer that has spread to other organs, is incurable. In new research published in the journal *Science*, Roswell Park Cancer Institute scientists have identified two gatekeeper genes that allow prostate cancer to progress and resist treatment. Their

work illuminates the mechanisms behind lineage plasticity, the ability of prostate cancer to adapt to therapy, and highlights opportunities to disrupt and even reverse this deadly process.

"Androgen-deprivation therapy is commonly used to treat patients whose prostate cancer has spread beyond the prostate. While most men initially respond to this therapy, the cancer nearly always returns and is often aggressive and lethal. We have discovered a mechanism that causes progression to this aggressive form of prostate cancer, providing a new opportunity to prevent or treat lethal forms of prostate cancer," says co-senior author David Goodrich, PhD, Professor of Oncology in the Department of Pharmacology and Therapeutics at Roswell Park.

"Importantly, these findings offer a new understanding of prostate cancer lineage plasticity, which involves the conversion of cancer cells that are dependent on a specific therapeutic target to cancer cells that are now indifferent to that target's function," adds co-senior author Leigh Ellis, PhD, Assistant Professor of Oncology in the Department of Pharmacology and Therapeutics. "This discovery offers the possibility to reverse or delay lineage plasticity, thereby prolonging the effectiveness of the currently used therapies, like androgen deprivation. And this new understanding has the potential to be applicable in other types of cancers."

Using preclinical models, the scientists demonstrated that loss of the tumor-suppressor gene known as Rb1 induces lineage plasticity and metastatic progression of prostate cancer. They also show that increased expression of another gene, Ezh2, is associated with lineage plasticity and may be therapeutically exploited. Treatment of resistant tumors with drugs that inhibit the Ezh2 gene may resensitize prostate cancer to androgen-deprivation therapy. The team expects to pursue these findings further in clinical studies at Roswell Park.

More information: "Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance," *Science*, science.sciencemag.org/cgi/doi … 1126/science.aah4199

Provided by Roswell Park Cancer Institute