Personalized combination treatment turns on an immunometabolic switch to effectively control aggressive prostate cancer

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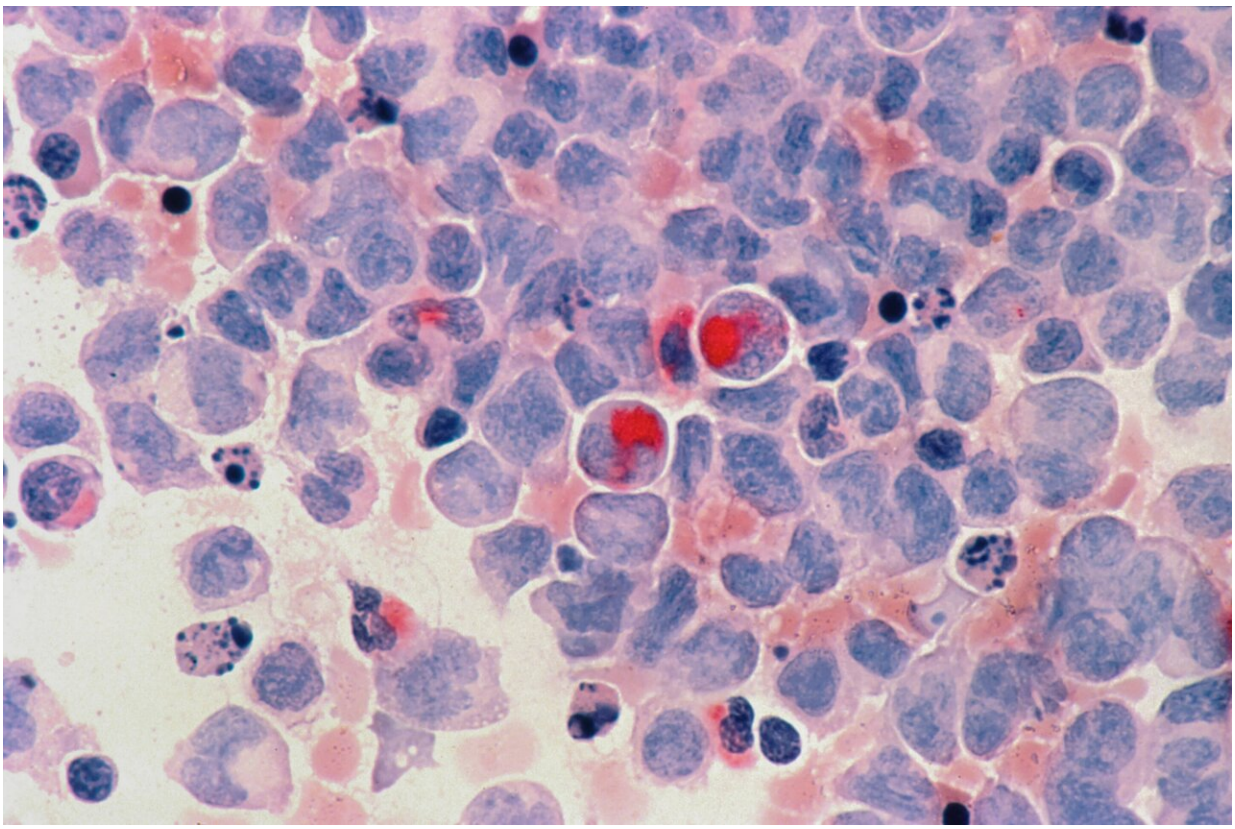

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Researchers at the University of Chicago Medicine Comprehensive Cancer Center established "proof-of-concept" for a new treatment

approach that was able to effectively treat the most aggressive forms of prostate cancer. The treatment showed complete tumor control and long-lasting survival without side effects in a mouse model of advanced prostate cancer.

These findings, which were published in *Clinical Cancer Research*, warrant further investigation in human clinical trials, the researchers concluded.

Strategies to overcome resistance

"Prostate cancer in the metastatic setting is a hormonally driven disease, and thus is typically treated with androgen deprivation therapy (ADT) to lower testosterone levels," said Akash Patnaik, MD, Ph.D., MMSc, an accomplished physician-scientist and internationally-recognized expert in prostate cancer research and treatment, who is the senior author of the publication.

"Although this form of treatment has been shown to have significant anti-cancer responses in patients, the majority will become resistant to hormonal therapy, or castrate-resistant."

Advanced prostate cancers that don't respond to standard hormone-based therapy, chemotherapy and immunotherapy leave patients with very few options. The development of treatments for these aggressive cancers known as metastatic castrate-resistant prostate cancer (mCRPC) represents an area of critical unmet need.

Patnaik's lab develops targeted therapeutic strategies to improve the responsiveness of prostate cancer to immunotherapy. They discovered that the immune system can often promote the growth of cancer—instead of suppressing it—through recruitment of abnormal tumor-associated macrophages that express PD-1 (a checkpoint

molecule which turns off an anti-cancer immune response) into the tumor microenvironment.

In a study published in March 2023, Patnaik and colleagues found that co-targeting the PI3K and PD-1 pathway enhanced the antitumor effects of ADT in PTEN-deficient prostate cancer, which is an aggressive form of advanced prostate cancer that results from the loss of a particular gene that keeps cell growth in check.

However, they observed that their strategy significantly enhanced the response rate for 60% of the mice, but 40% remained resistant to the therapy. The team conducted follow-up studies and found that activation of Wnt/β-catenin pathway restored lactate production in the treatment-resistant cancers, which they discovered drives the tumor-promoting properties of macrophages.

A paradigm shift

During the course of their studies, they discovered that lactate can crosstalk with macrophages and modify them via process called histone lactylation. This change makes the macrophages immunosuppressive, so they promote the growth of the cancer rather than suppress it.

In the current study, they discovered that resistance to PI3K inhibitors is mediated by Wnt/β-catenin and MEK signaling pathways. They co-targeted PI3Ki/MEK signaling pathways, which resulted in an 80% response rate. They observed that the 20% non-responders had a similar feedback activation of Wnt/β-catenin signaling.

They then tested a therapy regimen that consisted of three drugs targeting the PI3K, MEK, and Wnt/β-catenin signaling pathways. This brought the response rate to 100%.

"We were concerned about toxicity with continuous drug administration over the long-term, as is often the case with drug combinations in patients, so we did survival studies in mice with intermittent dosing of the same three drugs," Patnaik said.

The researchers were excited to see that the intermittent dosing schedule resulted in complete tumor control and significantly prolonged survival without long-term toxicity associated with continuous drug administration.

Patnaik says collectively, their findings provide "proof-of-concept" that targeting lactate as a macrophage phagocytic checkpoint controls the growth of PTEN/p53-deficient prostate cancer and warrant further investigation in clinical trials.

Moreover, the idea that the drugs can perturb signaling pathways in the cancer cells that affect the metabolic output of the cancer cell and cross-talk with tumor-promoting macrophages unveils new therapeutic opportunities that have not been previously pursued.

"We don't necessarily need to use targeted therapies to kill cancer cells but instead harness their ability to flip the switch in macrophages," Patnaik said. "Now the macrophages can eat the cancer cells and control the cancer."

Patnaik said the next step in this research would be testing this concept in the clinic. "We would develop a phase 1 clinical trial looking at testing an intermittent dosing approach to see if we can achieve a similar immune-activating and anti-tumor response as we've seen in our mouse model."

More information: Kiranj Chaudagar et al, Suppression of tumor cell lactate-generating signaling pathways eradicates murine