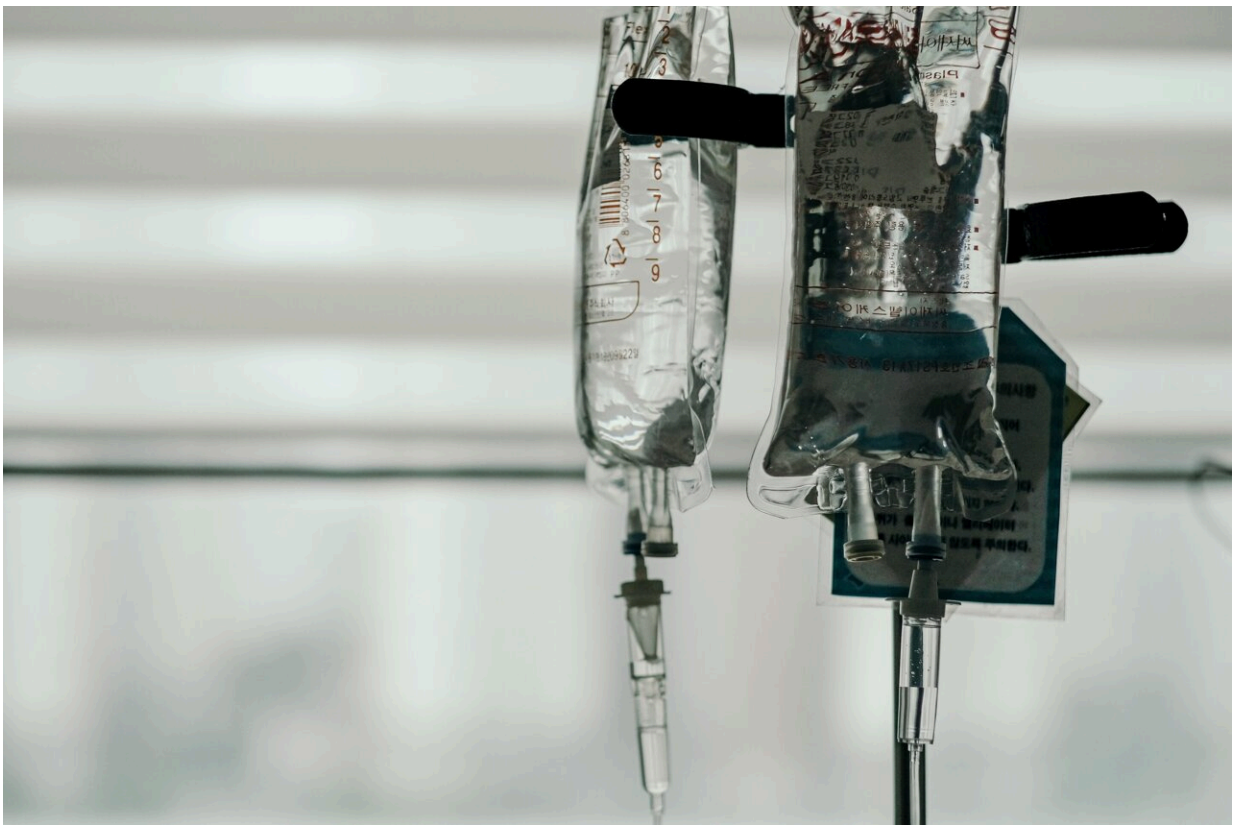
Newly identified personalized immunotherapy combination treats an aggressive form of advanced prostate cancer

March 3 2023



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Immunotherapies have been successful in treating many cancer conditions; however, not much success has yet been achieved in

metastatic castrate-resistant prostate cancer (mCRPC). A study published March 2 in *Clinical Cancer Research* has revealed new insights into why immunotherapies don't tend to work as well in prostate cancer.

The team, led by Akash Patnaik, MD, Ph.D., Assistant Professor of Medicine at the University of Chicago Medicine Comprehensive Cancer Center, discovered that the immune system promotes the growth of cancer instead of suppressing it through recruitment of abnormal tumor-associated macrophages (TAM) that express PD-1 into the tumor microenvironment.

Therapy resistance spells trouble for treatment

Hormonal therapies such as androgen deprivation therapy (ADT) and chemotherapies are first-line treatment options for treating metastatic prostate cancer. Although these therapies can improve the odds of survival, most patients will find their cancer returning. Chemohormonal therapies can also contribute to the development of aggressive forms of treatment-resistant prostate cancer.

One such aggressive form of advanced prostate cancer results from the loss of a particular gene called Phosphatase and tensin homolog (PTEN), which drives hyperactivation of phosphatidylinositol kinase-3 (PI3K) growth and survival pathway. As a result, cancer cells grow out of control.

"Given that PTEN/PI3K pathway alterations are one of the most frequent 'drivers' of human disease across all cancers, there have been several pharmaceutical efforts to target this pathway over the past decade. However, single-agent responses have been very limited to date," said Patnaik.

Recent clinical studies have found that PI3K inhibitors in combination

with ADT in mCRPC patients have only limited efficacy. To understand the mechanisms underlying the response and resistance to combinatorial ADT/PI3K inhibitors, Patnaik and his team performed simultaneous preclinical studies at in a PTEN-deficient mouse model which also lacked p53, another common alteration in human cancer that drives aggressive disease.

They discovered that PD-1-expressing immunosuppressive TAM were recruited following ADT/PI3K inhibitor treatment and blocked anti-cancer immunity mediated by macrophages. To test whether blocking PD-1 would increase the anti-tumor efficacy, PD-1 checkpoint immunotherapy was added to the ADT/PI3K inhibitor combination. The results showed a significantly increased overall response rate in mice.

The role of metabolic pathways

The ways in which cells consume and use energy, called metabolic pathways, play a key role in driving aggressive tumors like mCRPC to grow and spread uncontrollably, especially with hyperactivated PI3K pathways in PTEN-deficient context. In the current study, the team found that blocking PI3K suppresses lactate—a byproduct from glucose metabolism. Further investigation showed that tumor cells crosstalk with macrophages via lactate, which reprograms the macrophages to promote the growth of the cancer.

"While we were initially surprised that blocking the PI3K pathway in PTEN-deficient cancer cells did not kill them in a petri dish, we quickly discovered that it blocked the ability of cancer cells to educate macrophages via lactate. The disabled lactate-mediated communication flipped the switch in these cancer-promoting macrophages, so they have enhanced ability to eat cancer cells," said Patnaik.

Unfortunately, PI3K inhibitors alone are insufficient, because cancers

have figured out many ways to escape immune attacks and develop immune resistance. So, the team tested a combination therapy of ADT and PI3K inhibition in PTEN/p53-deficient mice and observed modest responses similar to what was seen in clinical trials. The insufficient response was driven by the recruitment of PD-1-expressing macrophages that can suppress a potent anti-tumor response.

Wnt signaling as a driving force for lactate

To test whether blocking PD-1 could increase the anti-tumor effects of the combined therapy, the team tried adding PD-1 blockers. They observed a significantly enhanced 60% response rate with the triple combination in mice, but 40% remained resistant to the therapy.

To determine why 40% of the cases remained resistant to treatment, the team conducted follow-up experiments and found that there is an activation of Wnt/β-catenin pathway that restored lactate production in the treatment-resistant cases.

"It's all coming down to cancer cells being evolutionarily hard-wired to preserve lactate protection, which has profound implications for macrophage-mediated anti-cancer immunity" added Patnaik. "The findings from our study demonstrate the importance of disrupting immunometabolic pathways in PTEN deficient cancers, to find sustainable solutions for these aggressive cancer types."

According to Patnaik, the right combination of therapies like PD-1 blockers with ADT and PI3K inhibitors can bring more success when treating aggressive PTEN-deficient prostate cancers that don't respond to conventional therapies.

A phase 1b clinical trial is being planned to test the safety and efficacy of PI3K/AKT pathway-blocking medicines in combination with an anti-

PD1 drug in patients with PTEN-deficient mCRPC. The effects of this treatment on immune cell activities will be studied. If successful, this project could result in a new precision immunotherapy regimen for patients with PTEN-deficient CRPC.

"These findings represent an exciting new opportunity to prevent prostate cancer cells from evading the immune system and a promising combination therapy for metastatic castration-resistant prostate cancer," said Howard R. Soule, Ph.D., Executive Vice President and Chief Science Officer of the Prostate Cancer Foundation. "PCF commends Dr. Patnaik and the research team on their achievement and proudly supports their work to bring us closer to our mission to eliminate death and suffering from prostate cancer."

More information: Kiranj Chaudagar et al, Reversal of lactate and PD-1-mediated macrophage immunosuppression controls growth of PTEN/p53-deficient prostate cancer, *Clinical Cancer Research* (2023). DOI: 10.1158/1078-0432.CCR-22-3350

Provided by University of Chicago Medical Center