Study provides path for new immunotherapy approaches to prostate cancer

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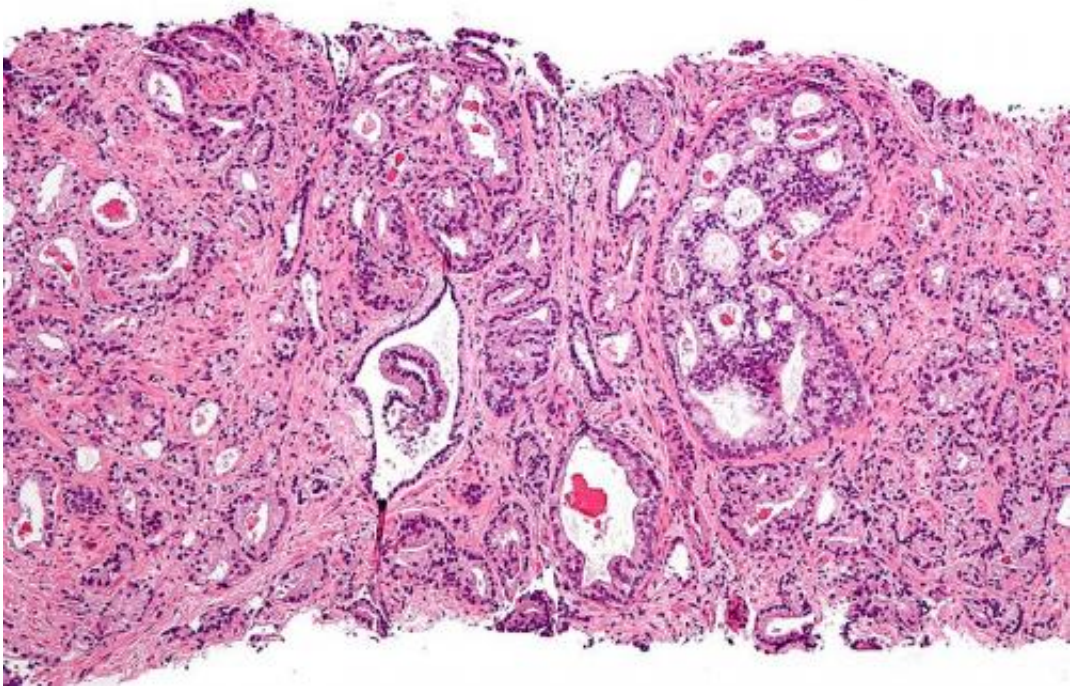

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

Prostate cancer, notoriously resistant to immunotherapy due to its immunologically cool nature, triggers two pathways to chill an immune attack after one immunotherapy drug fires up the immune system, researchers at The University of Texas MD Anderson Cancer Center report in *Nature Medicine*.

Based on their findings, the researchers launched a clinical trial for stage IV prostate cancer in March combining two drugs that target separate brakes on the immune system. The checkpoint inhibitors largely failed individually against the disease. Their results also implicate for the first time on a human tumor a third brake called VISTA in potentially inhibiting immune response.

"We've known that prostate cancer is immunologically cold, or quiet, with very little penetration of the tumors or their surrounding microenvironment by immune cells," said study leader Padmanee Sharma, M.D., Ph.D., professor of Genitourinary Medical Oncology and Immunology.

"Our study explored whether we could increase immune cell infiltration by combining the anti-hormonal drug Lupron with two rounds of the checkpoint inhibitor ipilimumab before surgery in patients with locally advanced prostate cancer," Sharma said.

Immune checkpoint inhibitors treat T cells, white blood cells that are the immune system's targeted weapons, freeing them to attack tumors by blocking proteins on the T cells' surface that shut them down. Ipilimumab blocks CTLA4 on T cells, the first known immune checkpoint, unleashing them to attack. "Untreated prostate cancer is largely a desert for T cells," said co-author Jim Allison, Ph.D., chair of Immunology.

Ipilimumab brings T cells in, but activates PD-L1

Immune analysis of the surgically removed tumors showed high levels of penetration of the tumors by activated T cells. "But we didn't see any complete responses among 16 prostate cancer patients, so we suspected other immune-inhibiting mechanisms had come into play," Sharma said.

Genomic and immune analysis of the tumors found increased levels of immune-suppressing PD-L1 and VISTA. T cells and other immune cells found in the tumors also had both proteins elevated.

PD-L1 connects with the immune checkpoint PD1 on T cells, activating PD1 to shut down the T cell. A number of drugs blocking PD1 are approved for advanced melanoma, Hodgkin lymphoma, lung, kidney, bladder and head and neck cancers. PD1 inhibitors don't work where there is no pre-existing T cell penetration of tumors.

"We concluded that driving T cells into the tumors would be step one, but then the next step would be to block PD-L1 and VISTA," Sharma said.

These results underpin the immunotherapy combination clinical trial: ipilimumab to bring T cells into the tumor, and the PD1 inhibitor nivolumab to defeat the PD-L1/PD1 response that follows. The trial, led by Sharma, will enroll 90 patients at nine centers nationally.

Six therapies approved for treating metastatic, castration-resistant prostate cancer extend survival but none provide durable responses. Nivolumab failed to provide any responses in a small clinical trial. While ipilimumab fell short of proving survival benefit in two phase III clinical trials, a small group of patients had long-term responses.

Targeting VISTA

VISTA has been shown to block immune response in mouse models of human cancer. And the team confirmed in lab studies that an antibody to knock down VISTA freed T cells to attack cancer cells.

An inhibitor for VISTA is in phase I clinical trial to gauge safety and dose, but Sharma notes the drug could also be combined in prostate

cancer clinical trials after the phase I is completed.

The ligand that activates VISTA has not been identified, Allison said. The team's findings represent the first report of VISTA expression on T cells in human tumors.

Unhelpful macrophages

The researchers also found that white blood cells called macrophages - Latin for "big eaters"—are also affected by ipilimumab treatment. Macrophages engulf and digest microbes, bits of cellular debris, tumor cells and other odds and ends as part of immune response.

They are also bipolar. In their M1 form, they actively assist immune response. In M2, they are in repair mode, helping post-immune recovery. The M2 mode promotes cancer growth and survival.Sharma, Allison and colleagues found that macrophages after ipilimumab treatment expressed lots of PD-L1 and VISTA and were in M2 mode.

Serial immune monitoring

"This paper highlights the importance of studying immune response longitudinally," Sharma said. "Observing immune response at one point in time doesn't reflect what's going on because the immune system is so dynamic. So baseline sampling in prostate tumors shows minimal immune infiltrate. You can change that with ipilimumab, but what else changes becomes incredibly important.

"Understanding these changes using post-treatment or on-treatment biopsies is important to develop rational combination strategies for these immune-modulating drugs," she said.The presurgical clinical trials, also called window of opportunity trials, allow researchers to learn a lot from a small number of patients to guide the design of larger trials, Sharma

said.

Immune monitoring of serial biopsies taken before, during and after treatment is a central aspect of MD Anderson's Immunotherapy Platform, which is co-led by Sharma and Allison and provides immune monitoring for 100 clinical trials. The platform is part of MD Anderson's Moon Shots Program to accelerate development of new treatment, prevention and early detection based on scientific advances.

Patient response

In the Lupron-ipilimumab trial, 17 patients participated in the trial, 16 completed treatment and surgery and one died of a cardiac complication before surgery. Six patients had their cancer progress and 10 were without evidence of progression for at least 3.5 years. All 16 remained alive 3.5 years after surgery.

All 17 experienced an immune-related adverse event, with eight experiencing the most serious grade 3 or 4 side effects, including inflammation of the colon, pancreas or pituitary gland and elevated transaminase enzymes in the liver. All were treated with corticosteroids and other immune-suppressive drugs.

The ipilimumab-nivolumab combination is in use in clinical trials for other cancers, most prominently for metastatic melanoma. In a 937-patient randomized trial, the combination provided an overall response rate of 57.7 percent, surpassing either drug alone in response rate and progression-free survival. And 55 percent of patients on the combination experienced a grade 3 or 4 adverse event related to treatment. The prostate combination trial has protocols for recognizing and treating immune-related adverse events.

More information: VISTA is an inhibitory immune checkpoint that is

increased after ipilimumab therapy in patients with prostate cancer, *Nature Medicine*, nature.com/articles/doi:10.1038/nm.4308