Medical Xpress

Study shows drug helps reprogram macrophage immune cells, suppress prostate and bladder tumor growth

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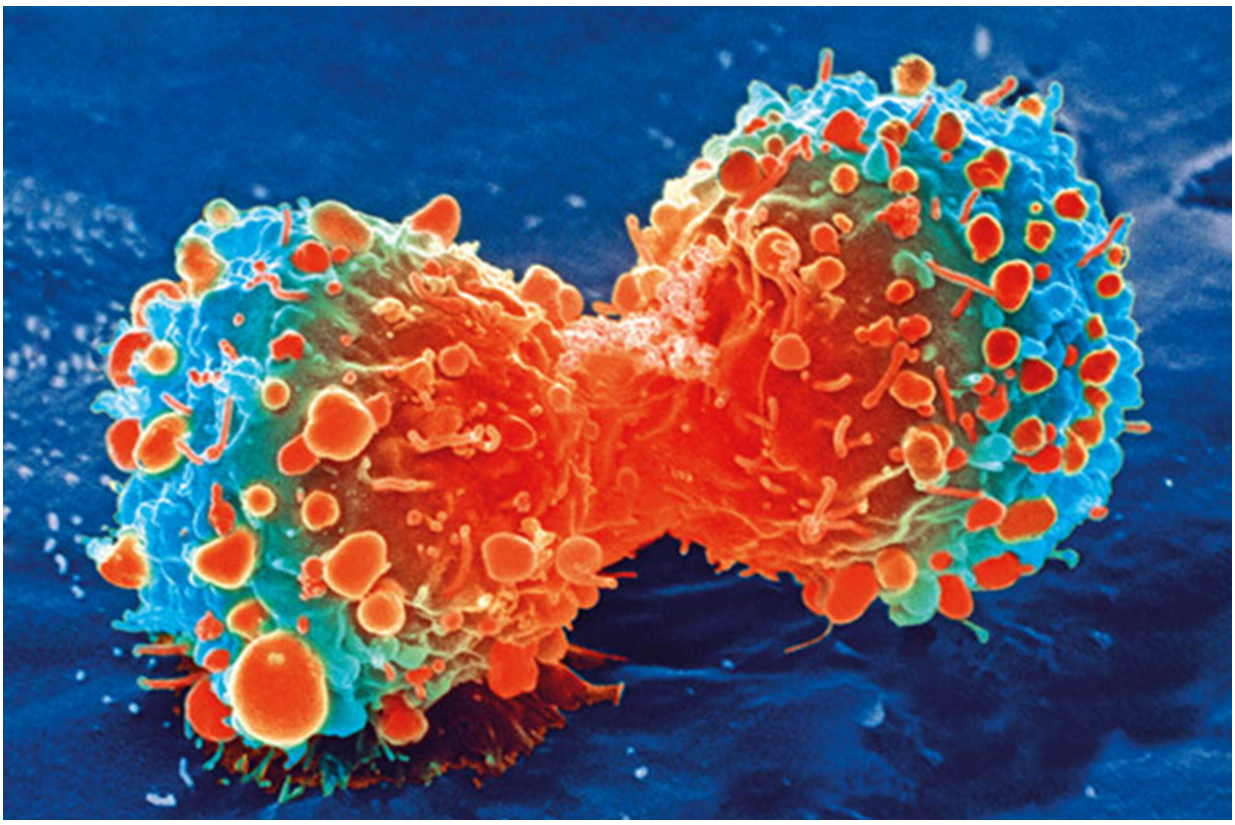

Cancer cell during cell division. Credit: National Institutes of Health

A novel therapy that reprograms immune cells to promote antitumor activity helped shrink hard-to-treat prostate and bladder cancers in mice,

according to research from the Johns Hopkins Kimmel Cancer Center and its Bloomberg~Kimmel Institute for Cancer Immunotherapy and Johns Hopkins Drug Discovery.

The study was published online May 3 in the journal *Cancer Immunology Research*.

Immunotherapies that help the immune system recognize and fight tumors have revolutionized care for many types of cancer. However, these therapies, which ramp up the production and activation of tumor cell-killing immune cells called T-cells, have not been effective in aggressive forms of prostate and bladder cancers.

The field of oncology has been trying to find out why and how to make immunotherapies work better in these cancers, explains the study's senior author, Jelani Zarif, Ph.D., Robert E. Meyerhoff Endowed Professor and associate professor of oncology at Johns Hopkins. Zarif and his colleagues suspected that immune cells called macrophages were to blame. Under some conditions, macrophages help tumors grow and suppress T-cell activity, hampering the immune response to cancers.

"The focus of our work is to reprogram the immune-suppressive tumor-associated macrophages into anticancer immune cells to enhance therapeutic responses to immunotherapies and other standard-of-care cancer therapies," Zarif says.

The immune-suppressing macrophages rely on the amino acid glutamine. Zarif and his colleagues previously demonstrated that macrophage precursor cells called monocytes will develop into immune-activating macrophages if they are grown in a laboratory setting without glutamine. By contrast, when monocytes are grown with glutamine, they become immune-suppressing macrophages.

Zarif and his team hypothesized that drugs blocking the immune cells from accessing glutamine would shift the balance of macrophages toward the immune-stimulating type and help shrink tumors. Studies have shown that a drug called 6-diazo-5-oxo-L-norleucine (DON) that starves tumors of glutamine shrinks tumors that depend on glutamine to grow. But development of the drug as a therapy for cancer was abandoned decades ago because it was also toxic to the gastrointestinal system and caused harmful side effects.

Instead, Zarif tapped an experimental glutamine-blocking drug developed by study co-authors Barbara Slusher, Ph.D., director of Johns Hopkins Drug Discovery, and Jonathan Powell, M.D., Ph.D., former associate director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy. The drug, JHU083, is a type of molecule called a prodrug that cells inside the body convert into an active drug.

Specifically, JHU083 can only be turned into its active, glutamine-blocking form inside the tumor, preventing it from causing harmful side effects elsewhere in the body. Studies show the drug shrinks tumors, reduces cancer spread and increases survival in animals with cancers of the skin, colon, blood and brain, as well as certain treatment-resistant breast cancers.

"Barbara Slusher and her team changed the drug's chemistry so it can circulate inactive throughout the body, and it only becomes active when it gets inside cancer cells," Zarif explains. "Because the active form is only released to cancer cells, you can give a lower dose, further reducing the risk of side effects."

Zarif and his colleagues showed that JHU083 blocks the use of glutamine in prostate and bladder tumors in mice, reducing tumor growth and triggering tumor cell death. It also reprogrammed immune-suppressing macrophages into immune-boosting macrophages. The

macrophages themselves started destroying tumor cells. They also helped recruit tumor-killing T-cells and natural killer cells to the tumors.

Adding an immunotherapy called a checkpoint inhibitor, which boosts the activation of T-cells in tumors, did not increase the effects of JHU083. Zarif explained this is likely because there was already so much antitumor immune activity in the JHU083-treated tumors.

"JHU083 could be a promising anti-cancer therapy for tumors with immune-suppressing macrophages and too few T-cells," he says. "It might also be a promising agent for tumors that do not respond to checkpoint inhibitors."

Zarif plans to collaborate with colleagues at Johns Hopkins to launch a clinical trial of JHU083 in patients with treatment-resistant prostate or bladder cancer to see if it shrinks tumors and prevents metastasis. They also want to continue studying whether combining JHU083 with other treatments improves its effectiveness against tumors.

The study's other co-authors were Monali Praharaj, Fan Shen, Alex J. Lee, Liang Zhao, Thomas R. Nirschl, Debebe Theodros, Alok K. Singh, Xiaoxu Wang, Kenneth M. Adusei, Kara A. Lombardo, Raekwon A. Williams, Laura A. Sena, Elizabeth A. Thompson, Ada Tam, Srinivasan Yegnasubramanian, Edward J. Pearce, Robert D. Leone, Jesse Alt, Rana Rais and Drew M. Pardoll of Johns Hopkins.

More information: Monali Praharaj et al, Metabolic reprogramming of tumor-associated macrophages using glutamine antagonist JHU083 drives tumor immunity in myeloid-rich prostate and bladder cancer tumors, *Cancer Immunology Research* (2024). DOI: 10.1158/2326-6066.CIR-23-1105