Breast cancer study uncovers how macrophages may contribute to a therapeutic weak spot

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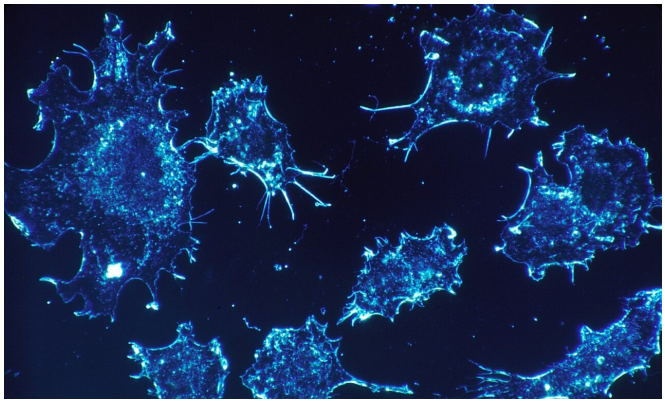

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Breast cancer, the second most common cancer in the United States, can result from a number of cellular misregulations, such as deficiencies in the DNA-repairing breast cancer gene, BRCA. Typically, BRCA-associated breast cancer is treated with poly ADP ribose polymerase (PARP) inhibitors and, recently, clinical trials have investigated pairing PARP inhibitor therapy with immunotherapy. Based on preclinical data, it is expected that the combination will recruit and activate T cells—immune cells that can kill tumor cells. Despite interest in this combination, researchers are already looking ahead for ways to get even more benefit from PARP inhibitors plus checkpoint inhibitors in breast cancer patients. That is precisely what a team of Dana-Farber/Brigham and Women's Cancer Center researchers have devoted their time to: identifying ways to boost the response to PARP inhibitors. The team found macrophage-mediated immune suppression to be the weak spot of PARP inhibition treatment. Findings are published in *Nature Cancer*.

"The question that drove our research was: How can we overcome PARP inhibitor resistance to turn this treatment into a homerun?" said Jennifer Guerriero, Ph.D., senior author and member of the Brigham's Division of Breast Surgery and director of the Dana-Farber Breast Tumor Immunology Laboratory. "Our findings suggest that there's something in the tumor microenvironment limiting the ability for T cells to be activated, and that something else is likely macrophages, which we found become highly suppressive after PARP inhibitor therapy."

Initial results of the combination of a PARP inhibitor and a checkpoint inhibitor in small numbers of patients with metastatic breast cancer have shown this combination to be active. A national pre-surgical trial led by DFCI investigators has recently opened and will examine this targeted combination in patients with genetic mutations sensitive to PARP inhibitors.

Similar to BRCA proteins, PARP proteins act to repair damaged DNA; in tumors, inhibiting DNA repairs means cancer cell death, so the combined elimination of BRCA and PARP repair mechanisms induce cancer cell death. PARP inhibitors recruit T cells, which are required for the body to recognize the presence of cancerous cells.

Like T cells, macrophages are another type of immune cell, which is recruited to wounds to patch them up. With cancer, macrophages are recruited to tumor sites, which are viewed as wounds to macrophages, and repair, strengthen, and, consequentially, exacerbate the tumor state. The team found an abundance of macrophages expressing a receptor necessary for their survival, CSF-1R, to be present in cancerous tissue after PARP inhibition treatment. Therefore, they hypothesized that targeting CSF-1R-positive

macrophages (a particularly suppressive macrophage type) in combination with PARP inhibition would lead to an enhanced anti-tumor response.

Since CSF-1R-positive macrophages exacerbate the tumor state, disabling these macrophages seemed an important therapeutic target for investigators. Using a triple-negative breast cancer BRCA-deficient mouse model, the team characterized these suppressive macrophages by assessing T cell and macrophage responses to different therapies and combinations of therapies.

When PARP and CSF-1R inhibition therapies were combined, there were dramatic anti-tumor responses seen with significant increase in overall survival. Furthermore, the triple combination of PARP inhibitor, CSF-1R inhibitor, and SREBP1 (a key regulator of lipid metabolism) inhibition was able to completely eliminate tumors in the aggressive triple-negative breast cancer mouse model. Researchers inferred from this therapeutic success that the PARP inhibitor directly activates macrophages to be suppressive in the tumor microenvironment.

While breast cancer tissue is often characterized before treatment, biopsies of tissue after treatment begins could provide more nuance to the characterization of these actors. Importantly, elucidating the mechanisms for PARP and macrophages will be critical in developing effective therapies and moving forward with clinical translation.

"At Dana-Farber/Brigham and Women's Cancer Center we have the opportunity to work closely with our clinical colleagues and ask these really important questions that will be critical to identify better biomarkers, so we can identify which patients will respond to which therapies," said Guerriero. "I am very optimistic about the use of PARP inhibitors—they are a game changer for patients with BRCA-deficient cancers, and their application is not just limited to breast cancers."

More information: Anita K. Mehta et al, Targeting immunosuppressive macrophages overcomes PARP inhibitor resistance in BRCA1-associated triple-negative breast cancer, *Nature Cancer* (2020). DOI: 10.1038/s43018-020-00148-7

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