Exercise benefit in breast cancer linked to improved immune responses

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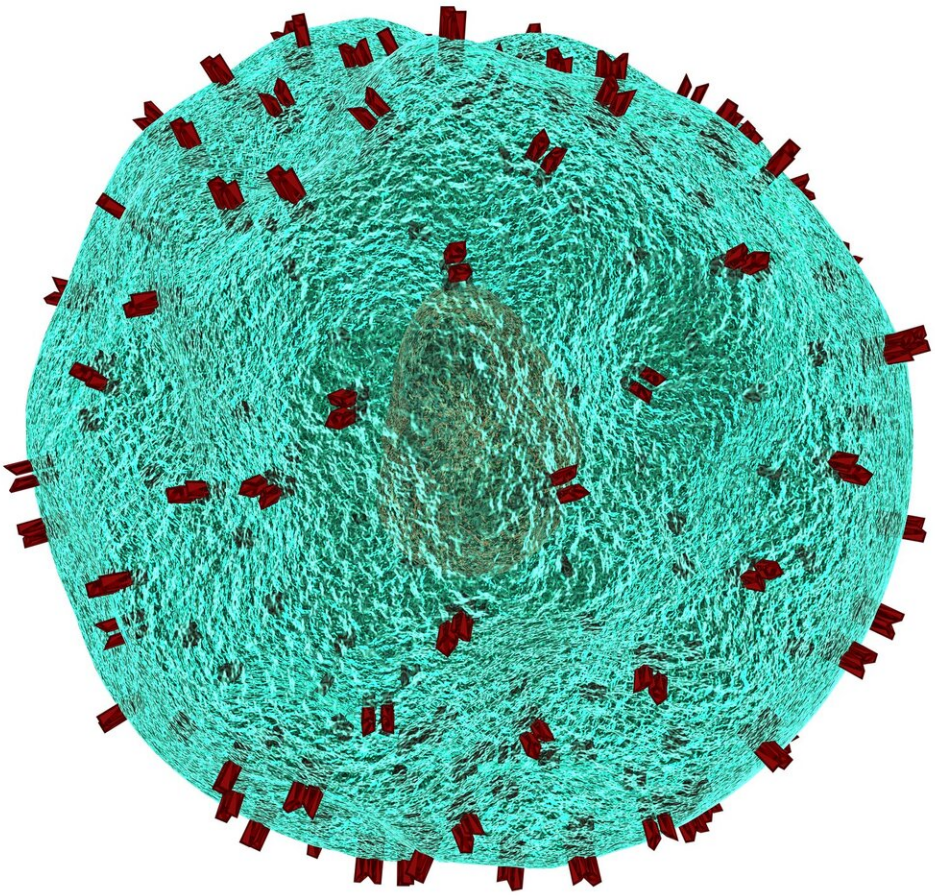

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Exercise training may slow tumor growth and improve outcomes for females with breast cancer—especially those treated with immunotherapy drugs—by stimulating naturally occurring immune mechanisms, researchers at Massachusetts General Hospital (MGH) and Harvard Medical School (HMS) have found.

Tumors in mouse models of human breast cancer grew more slowly in mice put through their paces in a structured aerobic exercise program than in sedentary mice, and the tumors in exercised mice exhibited an increased anti-tumor immune response.

"The most exciting finding was that exercise training brought into tumors immune cells capable of killing cancer cells known as cytotoxic T lymphocytes (CD8+ T cells) and activated them. With more of these cells, tumors grew more slowly in mice that performed exercise training," says co-corresponding author Dai Fukumura, MD, Ph.D., deputy director of the Edwin L. Steele Laboratories in the Department of Radiation Oncology at MGH.

As Fukumura and colleagues report in the journal *Cancer Immunology Research* , the beneficial effects of exercise training are dependent on CD8+ T cells; when the researchers depleted these cells in mice, tumors in mice that exercised no longer grew at a slower rate.

They also found evidence that recruitment of CD8+ T cells to tumors was dependent on two chemical recruiters (chemokines) labeled CXCL9 and CXCL11. Levels of these chemokines were increased in mice that exercised, and mice that were genetically engineered to lack the receptor (docking site) for these chemokines did not recruit CD8+ T cells and did

not have an anti-tumor benefit.

"Humans whose tumors have higher levels of CD8+ T cells tend to have a better prognosis, respond better to treatment, and have reduced risk of cancer recurrence compared with patients whose tumors have lower levels of the immune cells, effects that were echoed by a reduced incidence of metastasis, or spread, of the cancers in mice that exercised," says co-corresponding author Rakesh K. Jain, Ph.D., director of the Steele Labs at MGH and Andrew Werk Cook Professor of Radiation Oncology at HMS.

CD8+ T cells are also essential for the success of drugs known as immune checkpoint inhibitors, such as Keytruda (pembrolizumab), Opdivo (nivolumab) and Yervoy (ipilimumab), which have revolutionized therapy for many types of cancer, but have to date had only limited success in breast cancer. The researchers found that exercise-trained mice displayed a much better response to immune checkpoint blockade, while the drugs did not work at all in sedentary mice.

"We showed that daily sessions of a moderate-to-vigorous intensity, continuous aerobic exercise training, lasting 30-45 minutes per session, induces a profound reprogramming of the tumor microenvironment that rewires tumor immunity, recruiting and activating CD8+ T cells to an unprecedented level with a non-pharmacological approach. Similar exercise training could be prescribed to a patient referred to an exercise oncology program," says Igor L. Gomes-Santos, Ph.D., lead author and exercise physiologist and post-doctoral fellow in the Steele Labs.

He notes that current clinical guidelines focus on general wellness, improved fitness levels and quality of life, but not necessarily on improved cancer treatment, especially immunotherapy, and that this lack of evidence limits its application in clinical practice.

More convincing, mechanism-based data are needed to motivate oncologists to discuss exercise training with their patients, to motivate patients to become more active and to expand implementation of outpatient exercise oncology programs, the investigators say.

More information: Igor L Gomes-Santos et al, Exercise training improves tumor control by increasing CD8+ T-cell infiltration via CXCR3 signaling and sensitizes breast cancer to immune checkpoint blockade, *Cancer Immunology Research* (2021). DOI: 10.1158/2326-6066.CIR-20-0499

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