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Researchers discover how cancer cells that spread to lymph nodes avoid immune destruction

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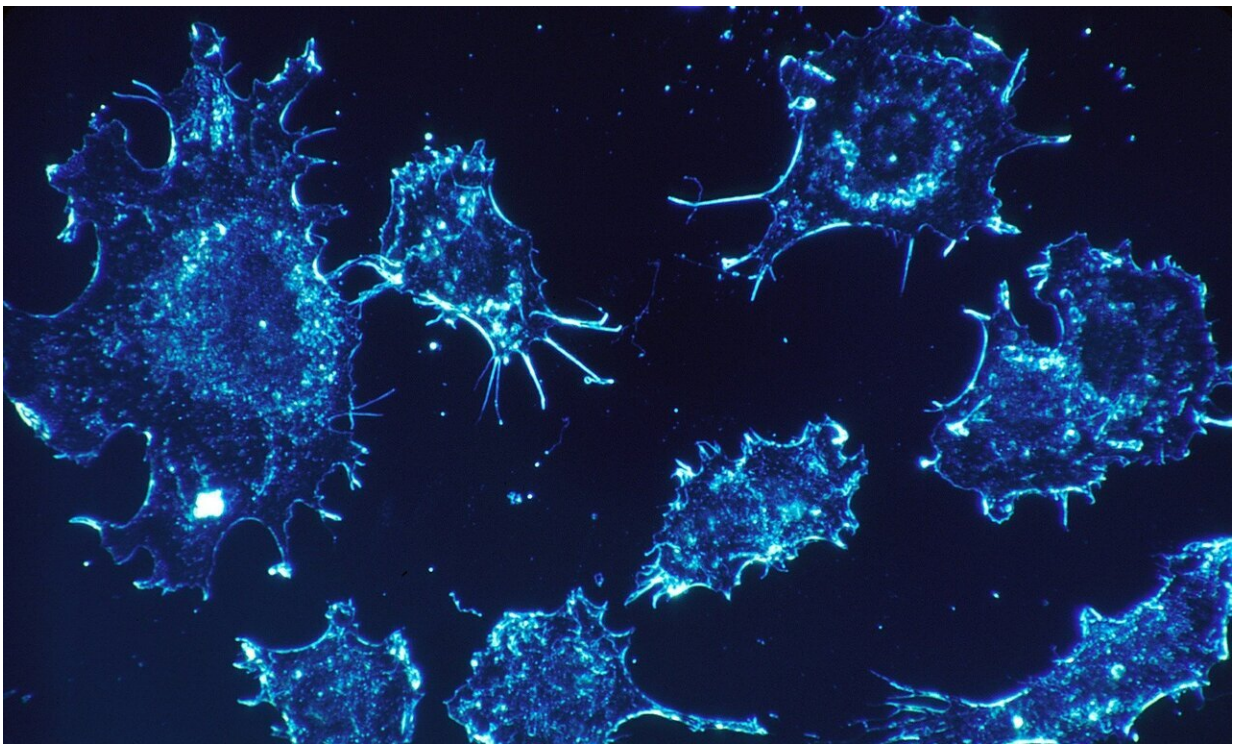

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Lymph nodes are critical to the body's immune response against tumors but paradoxically, cancer cells that spread, or metastasize, to lymph nodes can often avoid being eliminated by immune cells. Recent

experiments by investigators at Massachusetts General Hospital (MGH) and Boston University School of Medicine provide insights on the details behind this immune evasion, which could help scientists develop strategies to overcome it. The findings are published in *Nature Biomedical Engineering*.

"We know that lymph nodes are often the first place cancer spreads as it progresses. We also know that our immune system can attack and kill cancer cells," explains senior and co-corresponding author Timothy P. Padera, Ph.D., an investigator in Radiation Oncology at MGH and a 2021-2026 MGH Research Scholar. "One of the perplexing questions that has been at the core of the recent work in my lab is how can organs that generate our immune responses—lymph nodes—permit cancer cells to survive and take them over instead of attacking them? This was the driving motivation behind this study."

By analyzing patient tissue from breast, colon, and head and neck cancers, combined with animal models of breast cancer lymph node metastases, Padera and his colleagues showed that immune cells called T cells are abundant in metastatic lymph nodes but fail to penetrate tumors that have spread to such nodes. The team measured increased physical forces, known as solid stress, in lymph nodes with metastatic cancer. "We hypothesized that solid stress in lymph node tumors can impair both blood flow and the T cell trafficking capacity of blood vessels in lymph nodes," says lead and co-corresponding author Dennis Jones, Ph.D., an assistant professor of Pathology & Laboratory Medicine at the Boston University School of Medicine.

The scientists then developed a device to compress lymph nodes in order to simulate the gradual growth of lymph node metastases. When they applied compressive force to lymph nodes, there was a clear link between physical force and disruption of T cell entry into lymph nodes. "Our findings indicate that as cancer cells grow in the lymph node, they

reorganize and alter the lymph node, disabling critical functional responses of the immune system," says Padera. "By understanding how cancer cells are disabling lymph node function, we hope to fight back to help the lymph nodes generate anti-cancer immune responses, which will help fight cancer cells everywhere in the body."

Alleviating solid stress with the blood pressure drug losartan boosted the numbers of blood vessels and T cells in lymph node metastases, suggesting that alleviating solid stress is a potential strategy to improve T cell entry into tumors.

"Our work now leads to many important additional questions," says Jones. "Does losartan treatment combined with immunotherapy cause the eradication of metastatic cancer cells in lymph nodes by T cell killing? And further, does this lead to a strong systemic anti-cancer immune response that helps clear the cancer from the entire body?" Jones notes that finding the answers to these questions could lead to new treatment strategies for patients with metastatic cancer.

More information: Solid stress impairs lymphocyte infiltration into lymph-node metastases, *Nature Biomedical Engineering* (2021). DOI: 10.1038/s41551-021-00766-1 , www.nature.com/articles/s41551-021-00766-1

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