Potential new treatment strategy for breast cancer cells that have spread to the brain

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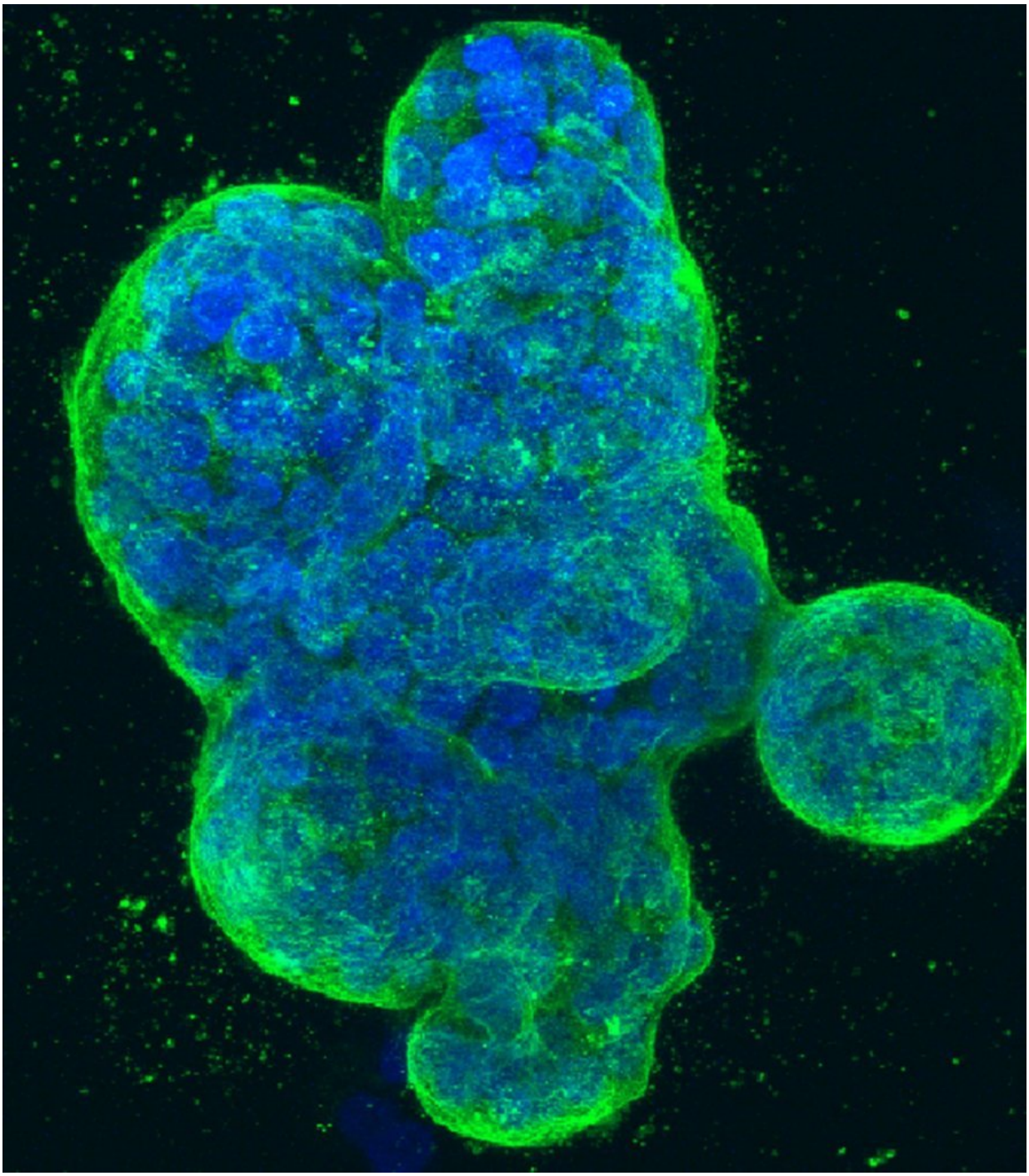

Three-dimensional culture of human breast cancer cells, with DNA stained blue and a protein in the cell surface membrane stained green. Image created in 2014 by Tom Misteli, Ph.D., and Karen Meaburn, Ph.D. at the NIH IRP.

New research reveals that when breast cancer cells spread to the brain, they must boost production of fatty acids, the building blocks of fat, in order to survive there. The work, which is published in *Nature Cancer* and was led by investigators at Massachusetts General Hospital (MGH) and the Koch Institute of the Massachusetts Institute of Technology (MIT), points to a potential new treatment target for shrinking brain tumors that arise secondary to breast cancer.

Therapies that target the human epidermal growth factor receptor 2 (HER2) have transformed treatment for patients with breast cancer whose tumor cells express HER2, but brain metastases from this disease are typically fatal because they are resistant to anti-cancer therapies that are effective in other locations in the body. This is in part due to the blood-brain barrier that protects the brain against circulating toxins and pathogens, but changes in the cancer cells once they reach the brain may also play a role.

Such changes may occur because cancer cells that metastasize to the brain encounter differences in nutrient availability in brain tissue relative to other tissues in the body. Therefore, the malignant cells may have to alter how and what they metabolize to support tumor survival and growth. To investigate this possibility, researchers designed experiments in mice that assessed how metabolism differs between breast tumors that traveled to the brain and other locations in the body.

The team found that access to fats is limited for breast tumors to grow in the brain. In response, fatty acid synthesis is elevated in these tumor cells, as a result of increased activity of an enzyme called fatty acid synthase. "Consistent with our preclinical findings, clinical specimens of brain metastases from patients over-express fatty acid synthase relative to tumors that have not metastasized," says co-lead author Gino Ferraro, Ph.D., a postdoctoral fellow in the E.L. Steele Laboratories for Tumor Biology at MGH.

The findings demonstrate that when a cancer has spread to a particular organ, potential treatment strategies could take advantage of the nutrient availability at that site. Inhibiting the cancer cells' ability to use that nutrient may lead to their demise.

"To date, targeted therapies mostly focus on genetic vulnerabilities of cancer cells. Our work demonstrates that the environment in which the cancer cells reside can also dictate metabolic vulnerabilities that should be considered during the development of treatment strategies," says co-corresponding author Rakesh K. Jain, Ph.D., director of the E.L. Steele Laboratories for Tumor Biology at MGH and the Andrew Werk Cook Professor of Radiation Oncology at Harvard Medical School.

The team notes that an inhibitor of fatty acid synthase, called TVB2166, is currently being evaluated in patients with metastatic breast cancer. "This compound is not brain-permeable, however, and patients with symptomatic brain metastases are excluded from these trials," says co-corresponding author Matthew Vander Heiden, MD, Ph.D., an associate director of the Koch Institute at MIT and a member of the Broad Institute of MIT and Harvard. "Therefore, the efficacy and safety of this strategy in patients with brain metastases remains to be explored using brain-penetrable fatty acid synthase inhibitors."

More information: Fatty acid synthesis is required for breast cancer brain metastasis, *Nature Cancer* (2021). DOI: 10.1038/s43018-021-00183-y

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