The sneaky way estrogen drives brain metastasis in non-estrogen-dependent breast cancers

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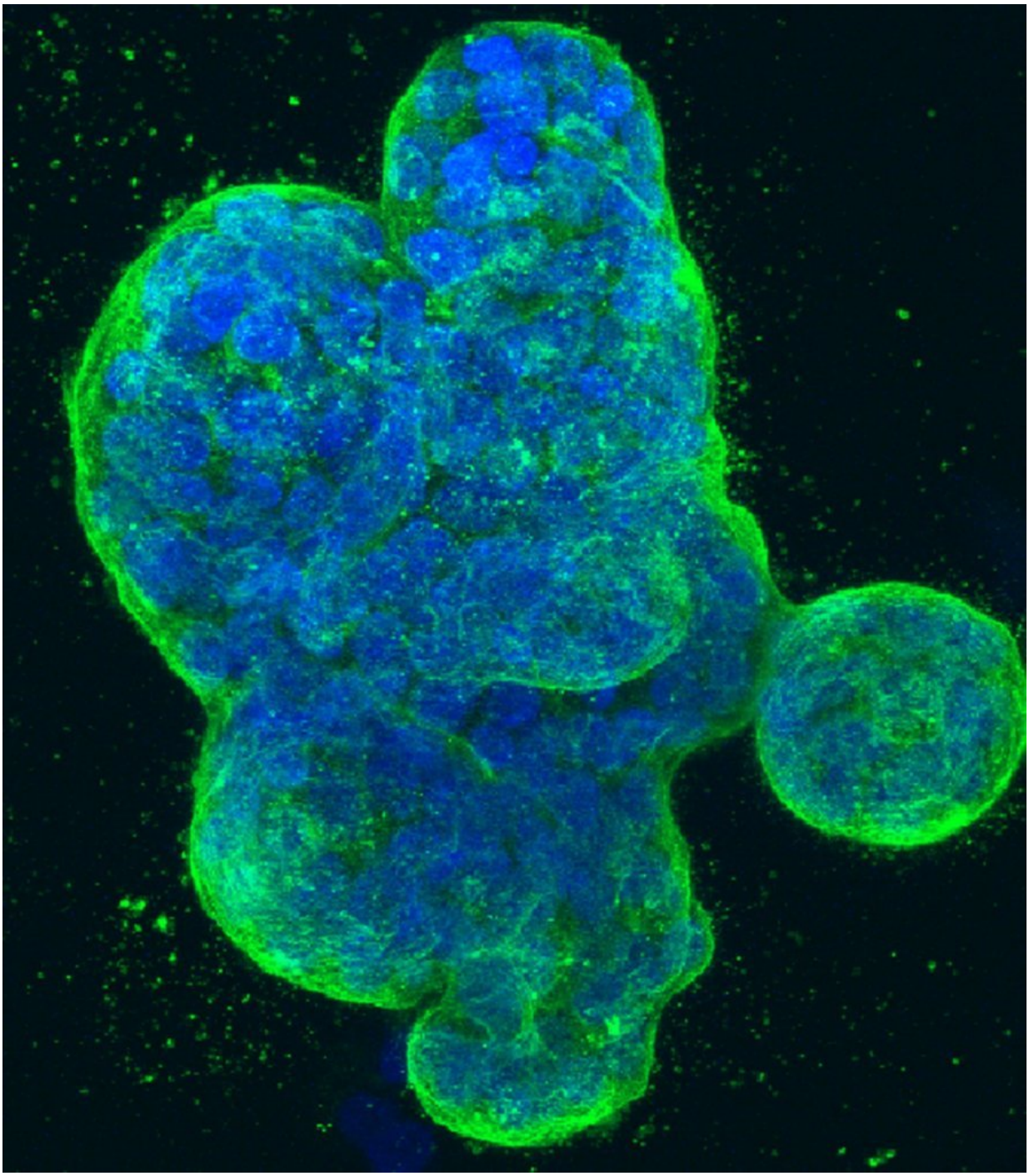

Three-dimensional culture of human breast cancer cells, with DNA stained blue and a protein in the cell surface membrane stained green. Image created in 2014 by Tom Misteli, Ph.D., and Karen Meaburn, Ph.D. at the NIH IRP.

Triple-negative breast cancers are more likely than other breast cancer types to metastasize and are especially likely to go the brain in younger women. Researchers have tested various hypotheses to explain this danger. One idea that has gotten little attention is the thought that estrogen might be to blame. After all, triple negative breast cancers lack estrogen receptors (along with progesterone receptors and HER2, thus the name triple negative), and so these cancers can't possibly be influenced by estrogen. Right?

Now a University of Colorado Cancer Center study published in the journal *Oncogene* shows that while estrogen doesn't directly affect triple-negative breast cancer cells, it can affect surrounding brain cells in ways that promote cancer cell migration and invasiveness. Importantly, the study also suggests ways to stop the activity of estrogen in the brain that fertilizes triple-negative breast cancer metastasis.

"The cancer cells aren't responsive to estrogen, but estrogen influences the microenvironment. We found that astrocytes—one of the main components of the microenvironment in the brain—are estrogen-responsive. When they are stimulated with estrogen, they produce chemokines, growth factors, and other things that promote brain metastasis," says Diana Cittelly, Ph.D., investigator at CU Cancer Center and assistant professor in the CU School of Medicine Department of Pathology.

Technically, Cittelly and colleagues including postdoctoral researcher, Maria Contreras-Zarate, Ph.D., found that estrogen induces astrocytes (brain cells) to produce growth factors called brain-derived neurotrophic factor (BDNF) and Epidermal Growth Factor (EGF), and that these factors turns on two genetic migration/invasion switches in cancer cells, namely TRKB and EGFR.

"This may explain why breast cancers diagnosed in younger women are

more likely to metastasize to the brain—pre-menopausal women have more estrogen, and it may be influencing the microenvironment of the brain in ways that aid cancer," Cittelly says.

Traditionally, estrogen-positive cancers have been treated with anti-estrogen receptor therapies including tamoxifen. However, it has always seemed obvious that cancers without estrogen receptors would not respond to anti-estrogen receptor therapy. And, unfortunately, there has been little opportunity to accidentally notice the effects of anti-estrogen therapy on brain metastases resulting from breast cancer.

"Historically, women with brain mets have been excluded from clinical trials due to overall poor prognosis," says Cittelly, pointing out that earning approval for a new drug requires showing its effectiveness, and even a promising drug may seem ineffective in patients whose cancer has already metastasized to the brain. "So we have never explored whether anti-estrogens will have benefit for these women. Our work shows there might be a benefit in anti-estrogen therapies in preventing brain metastasis in women with triple-negative breast cancer."

Additionally, Cittelly and colleagues recently received funding to explore interceding elsewhere in this chain of action that starts with estrogen and ends with brain metastasis. Basically, if estrogen works through EGFR or TRKB, it may be useful to inhibit EGFR and/or TRKB, alone or together, in these patients. Fortunately, like estrogen-receptor inhibitors, EGFR and TRK inhibitors already exist and are in use with other cancers, making testing these strategies dramatically more feasible.

"We are finally beginning to recognize the unique role of the microenvironment in the brain," Cittelly says. "Cancer metastasis may not depend on cancer cells alone. Stopping metastasis in these patients may require looking at the conditions of tissues that surround and

support cancers."

More information: Maria J. Contreras-Zárate et al, Estradiol induces BDNF/TrkB signaling in triple-negative breast cancer to promote brain metastases, *Oncogene* (2019). DOI: 10.1038/s41388-019-0756-z

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