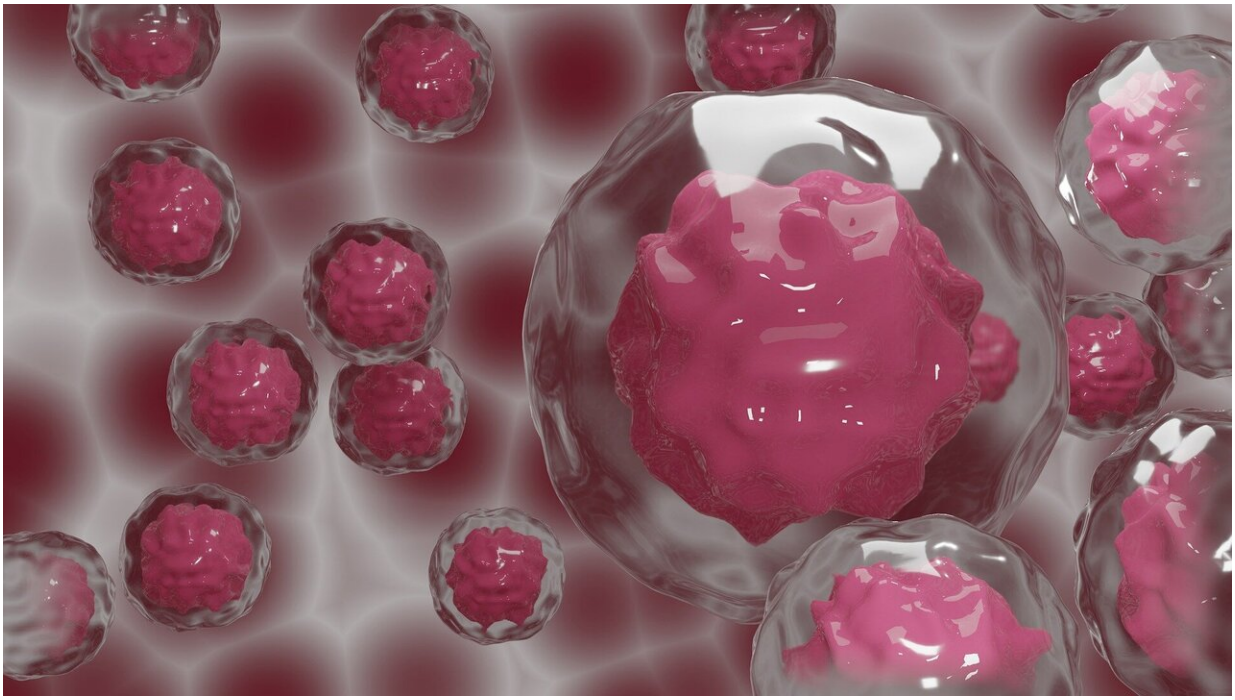
MedicalXpress

New insights about 'bad news' breast cancer mutation point to treatment opportunities

April 19 2022



Credit: CC0 Public Domain

A mutated gene found in more than 20% to 30% of breast cancer recurrences may help tumors become more aggressive and promote metastasis, according to a pair of new studies that uncover mechanisms behind these processes and point to new therapy targets.

"We're excited about this research because it addresses an important

clinical problem: A huge number of deaths in breast cancer patients are the result of mutations in estrogen receptor genes," said senior author Steffi Oesterreich, Ph.D., co-leader of the Cancer Biology Program at UPMC Hillman Cancer Center and professor in the University of Pittsburgh School of Medicine Department of Pharmacology & Chemical Biology. "Our study provides a deeper understanding of how these mutations contribute to disease progression and also identifies potential vulnerabilities, which we hope will lead to development of personalized treatment approaches."

More than 40,000 women die each year from breast cancer in the United States. About two-thirds of tumors express estrogen receptor genes. Hormone therapy can be very effective for these estrogen receptor-positive (ER+) tumors, but in about one-third of cases, the receptor becomes mutated and no longer responds to this treatment.

As a first step toward developing new therapies for these patients, the multi-institutional team led by Dr. Zheqi (Vaciry) Li, who was a postdoctoral associate in Oesterreich's lab, took a closer look at tumors harboring estrogen receptor gene ESR1 with a mutation at one of several "hotspots" in the genetic code.

In a new *Cancer Research* study, the researchers show that these hotspot mutations not only drive resistance to hormone therapy but also promote metastasis, helping breast cancer cells move to other parts of the body.

According to Oesterreich, ESR1 is a master regulator of several molecular pathways, including a type of interaction between cells called cell-cell attachment. When the researchers took liquid biopsies from patients with mutated ESR1, they found clusters of tumor cells circulating in the blood.

"We think that this mutation makes tumor cells sticky, so they clump

together," said Oesterreich, who is also co-director of the Women's Cancer Research Center, a collaboration between UPMC Hillman and Magee-Womens Research Institute. "This is a novel finding and somewhat unexpected."

The researchers suspect that these sticky clumps of cells are transported throughout the blood and adhere to healthy tissues, promoting new tumors, or metastases, in other parts of the body.

"This mutation is bad news for cancer prognosis, but the good news is that there are drugs that target cell-cell attachment," said Oesterreich. "We hope that this study lays the foundation to test drugs that prevent or treat metastatic breast cancer driven by estrogen receptor mutations."

In the second study, published today in *Nature Communications*, the researchers found that tumors with ESR1 mutations also had high expression of so-called basal features, which make breast cancers aggressive and difficult to treat.

But this study also offered a silver lining. Mutant tumors had high expression of genes associated with tumor infiltration by macrophages, a type of immune cell that cleans up dead cells and destroys bacteria and other pathogens.

"Previously, it was thought that ER+ tumors are cold, or impenetrable by immune cells, meaning that they don't respond to immunotherapy," explained Oesterreich. "But these findings give us a potential new target for patients with the ESR1 mutant breast cancer: Targeting macrophages could kill the tumor."

In ongoing work, Oesterreich and her team seek to confirm immune infiltration in ESR1 mutant tumors collected at other research centers. They are also collaborating with investigators from other institutions to

test whether cell-cell attachment involved in metastasis can be blocked with drugs.

More information: Zheqi Li et al, Hotspot ESR1 Mutations Are Multimodal and Contextual Modulators of Breast Cancer Metastasis, *Cancer Research* (2022). DOI: 10.1158/0008-5472.CAN-21-2576

Zheqi Li et al, ESR1 mutant breast cancers show elevated basal cytokeratins and immune activation, *Nature Communications* (2022). DOI: 10.1038/s41467-022-29498-9

Provided by University of Pittsburgh