Breast cancer cells found to switch molecular characteristics

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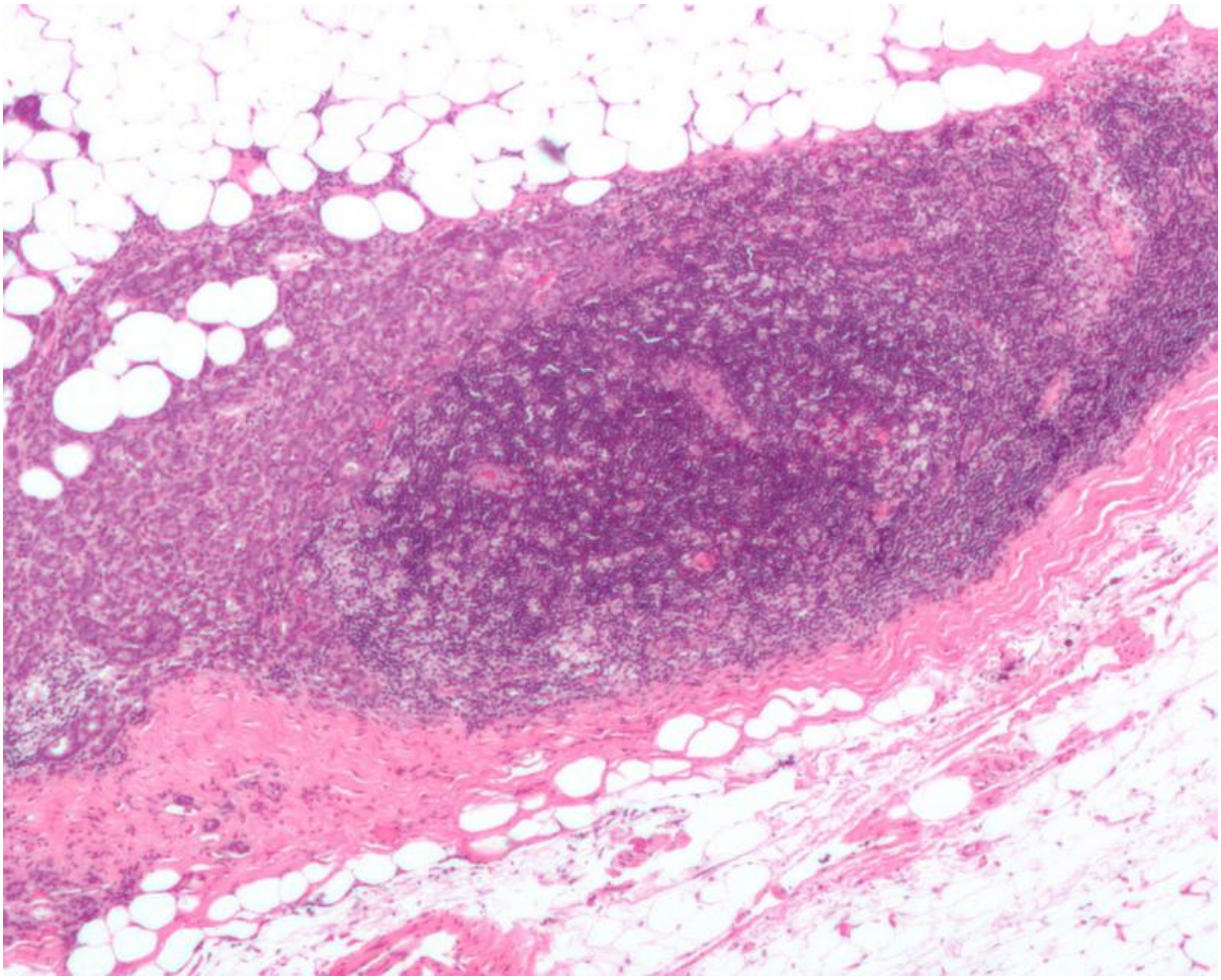

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

A study led by Massachusetts General Hospital (MGH) investigators reveals how spontaneous changes in the molecular characteristics of tumors can lead to tumors with a mixed population of cells requiring treatment with several types of therapeutic drugs. In their report in the Sept. 1 issue of *Nature*, the research team describes finding a mixture of HER2-positive and HER2-negative circulating tumors cells (CTCs) in blood samples from patients who developed metastatic disease after originally being diagnosed with estrogen-receptor (ER)-positive/HER2-negative breast cancer.

"Not only did we observe the acquisition of HER2 positivity in patients with ER-positive/HER2 negative breast tumors, we also found that this population of tumor cells is able to spontaneously oscillate between HER2-positive and HER2-negative states, which contributes to tumor progression and resistance," says Shyamala Maheswaran, PhD, of the MGH Cancer Center, co-senior author of the report. "We also showed in mouse models the types of therapies that may be most useful for patients with these difficult-to-treat tumors."

Molecular heterogeneity of tumors has become a confounding factor in cancer treatment in recent years, requiring the use of multiple drugs that specifically target all the different cell populations driving tumor growth. The current study was designed to investigate further the differences in HER2 expression that can occur in individual patients' tumors and how they affect tumor growth and treatment. Using the CTC-iChip - a microfluidic device developed at the MGH Center for Engineering in Medicine that isolates CTCs from blood samples - the researchers found both HER2-positive and HER2-negative CTCs in samples from 16 out of 18 patients who had developed metastases after treatment for ER-positive/HER2-negative breast cancer.

CTCs isolated from patients with ER-positive/HER2-negative breast cancer and grown in culture also showed a similar pattern of HER2

expression, in which some of the tumor cells expressed HER2 and some did not. Closer examination of these HER2-positive tumor cells showed elevated expression of proteins in several growth signaling pathways, but the level of HER2 expression was not as high as seen in HER2-amplified primary tumors.

These HER2-positive CTCs were no more sensitive to treatment with a HER2-inhibiting drug than were HER2-negative CTCs, but combined treatment with both the HER2 inhibitor and an IGFR1 (insulin-like growth factor receptor 1) inhibitor was toxic to HER2-positive CTCs. In contrast, HER2-negative CTCs had elevated expression of proteins in the Notch developmental pathway and in pathways that respond to DNA damage. Reflecting those differences, HER2-positive CTCs were found to proliferate more rapidly and respond to treatment with standard chemotherapy drugs, while HER2-negative CTCs were more resistant to chemotherapy drugs but sensitive to gamma secretase inhibitors, which are known to suppress Notch signaling.

Injecting either HER2-positive or HER2-negative breast tumor cells into the mammary tissue of mice led to the development of tumors with both types of cells. Treatment of tumors in which HER2-positive cells were predominant with the chemotherapy drug paclitaxel led to rapid tumor shrinkage, followed by recurrence with a greater number of HER2-negative cells, while paclitaxel treatment of tumors with more HER2-negative cells did not have any effect. Treating mice in which tumors had been initiated by a mixture of HER2-positive and HER2-negative tumor cells with a combination of paclitaxel and a gamma secretase inhibitor did delay tumor recurrence significantly, suggesting the potential utility of a combination treatment strategy to eliminate this mixed population of tumor cells.

"The ability of these two populations of tumor cells to convert back and forth highlights the importance of treating tumors with drugs that would

simultaneously target both populations," says Maheswaran, who is an associate professor of Surgery at Harvard Medical School. "Now we need to investigate the mechanisms responsible for this interconversion."

More information: Nicole Vincent Jordan et al, HER2 expression identifies dynamic functional states within circulating breast cancer cells, *Nature* (2016). DOI: 10.1038/nature19328

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