Protein may protect tumor-initiating breast cancer cells

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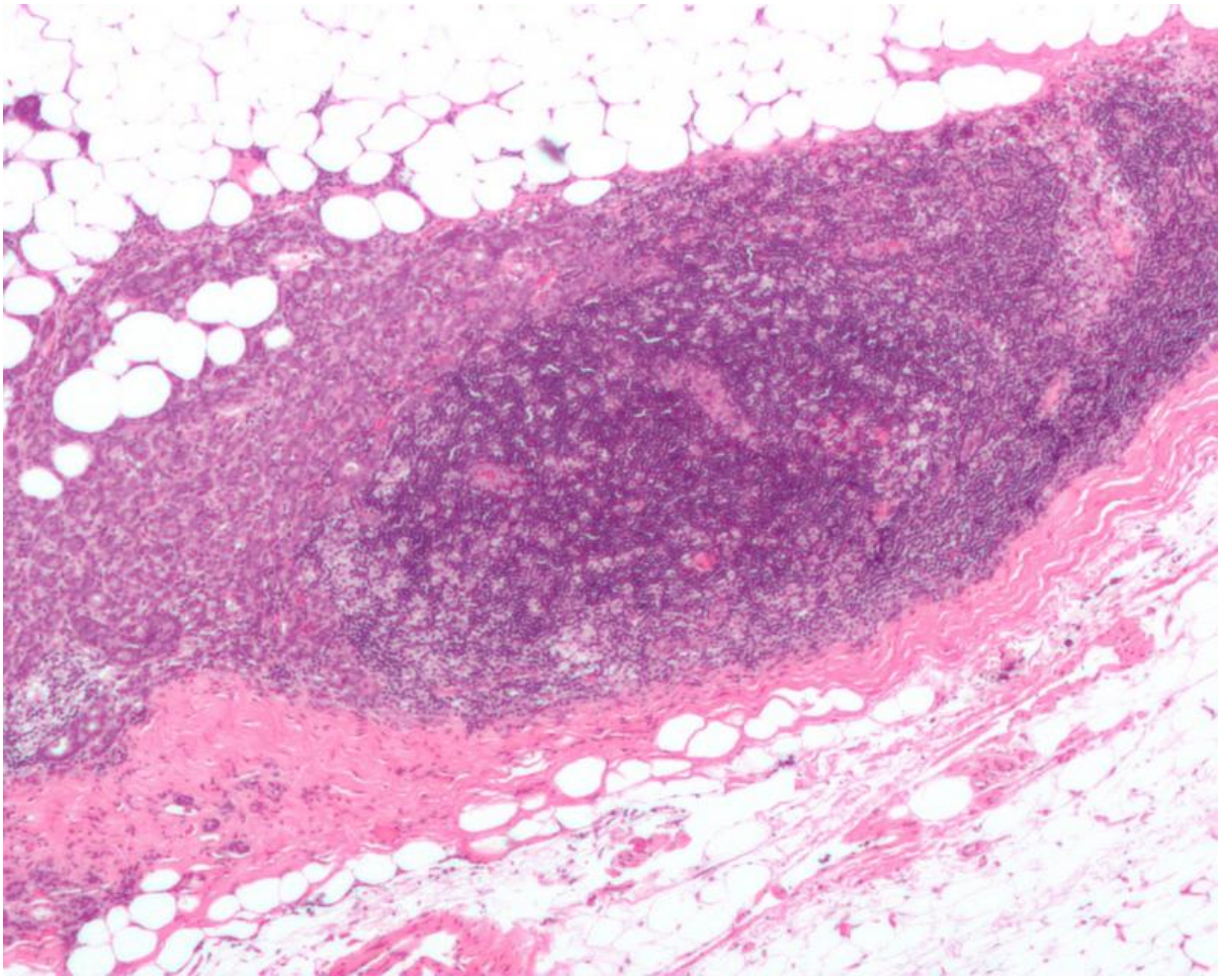

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Massachusetts General Hospital investigators have identified a protein that may play an essential role in maintaining a population of tumor-initiating cells (TICs)—treatment-resistant cells responsible for cancer recurrence and metastasis—in breast cancer, as well as a compound that appears to reduce the molecule's ability to protect TICs from the effects of chemotherapy. Results of the team's study are being published online in *PNAS*.

"The protein we have identified—G3BP2—affects the survival and proliferative potential of breast cancer cells by regulating the ratio of TICs to non-TICs within a tumor," says Igor Garkavtsev, MD, PhD, of the Steele Laboratories of Tumor Biology in the MGH Radiation Oncology Department, who led the study. "We also found that G3BP2 regulates breast tumor initiation in a way that leads to the increased expression of Oct-4 and Nanog, transcription factors contributing to the pluripotency of embryonic stem cells."

Breast cancers are made up of many different cell types, and it is believed that TICs, while making up a very small proportion of tumors, are capable of generating the full range of cancer cells. TICs may be present in most types of cancer; and since they seem to resist common therapies, finding ways to directly target TICs—which requires better understanding of the mechanisms by which they are generated and maintained—could significantly improve cancer treatment.

The MGH team began by treated a metastatic breast cancer cell line, which would be expected to contain a significant proportion of TICs, with combinations of the chemotherapy drug paclitaxel and compounds from a library of more than 60,000 diverse small molecules. From those compounds that increased the ability of paclitaxel to reduce the survival of cancer cells, they identified the one with the most pronounced effect, which they called compound C108.

Testing that compound in a different line of TIC-enriched breast cancer cells not only confirmed its ability to increase the toxic effect of paclitaxel but also showed that compound C108 alone could reduce the proportion of TICs in a population of cells. After implantation into mice, breast cancer cells that had been treated with compound C108 were observed to have an approximately 10-fold reduction in the proportion of TICs, compared with implanted cells that had been treated with an inert compound.

Further experiments showed that compound C108 exerts its effect through G3BP2, a protein found in cellular structures called stress granules, which are formed to protect RNA molecules from stresses such as oxygen deprivation or toxins - including chemotherapy drugs. Screening genetic samples from more than 4,000 breast cancer patients revealed that those with higher levels of G3BP2 expression had significantly worse outcomes, with increased tumor recurrence and metastasis.

More detailed analysis revealed that G3BP2 regulates breast tumor initiation by controlling the levels of TICs within tumors. The protein exert its effects by stabilizing the mRNA of SART3—a protein that plays a role in the pluripotency, the ability to give rise to any type of cell, of embryonic stem cells—leading to increased expression of pluripotency factors Oct-4 and Nanog.

"The possibility that some breast cancer cells with vast proliferative potential may be intrinsically resistant to standard therapies may partially explain why tumors relapse after treatment," says Garkavtsev, who is an assistant professor of Radiation Oncology at Harvard Medical School. "Our identification of compound C108 and the discovery of G3BP2 as a potential regulator of TICs open opportunities for further exploration of the mechanisms of breast cancer initiation and the development of novel therapies. Combining derivatives of compound C108 with standard

treatments could benefit patients with relapsed, drug-resistant or metastatic breast cancer and improve their survival."

More information: Stress granule-associated protein G3BP2 regulates breast tumor initiation, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1525387114

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