# Gene previously observed only in brain is important driver of metastatic breast cancer

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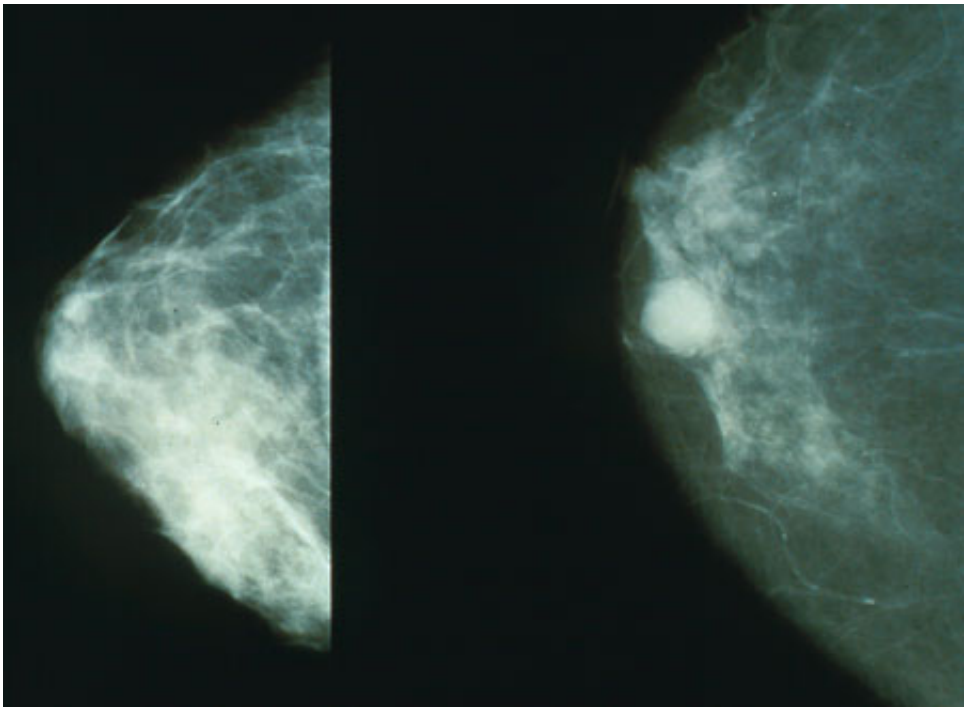

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

When breast cancer becomes advanced and spreads to other organs, patient survival is drastically reduced, prompting the need to explore the genes that may cause tumor cells to metastasize.

Now, scientists from The Wistar Institute have shown that one gene that was once thought only to be found in the brain is also expressed in breast

cancer and helps promote the growth and spread of the disease. Additionally, they showed how a version of the gene with edited RNA prevents metastasis. The findings were published online by the journal *Nature Communications*.

If breast cancer is caught in its earliest stages, all patients who are treated successfully are alive five years after treatment, according to the National Cancer Institute. However, when breast cancer metastasizes, or spreads from the breast to other organs, only about one in five patients survive more than five years. This significant gap in survival underscores the need to determine what causes breast cancer to spread. The causes of metastasis in breast cancer at a molecular level are not very well understood, so identifying regulatory genes that prompt this behavior could have a tremendous impact on survival, from early detection to the design of better treatment strategies.

"Metastatic breast cancer is ultimately what kills patients," said Qihong Huang, M.D., Ph.D., associate professor in the Tumor Microenvironment and Metastasis Program at The Wistar Institute and lead author of the study. "While early detection is critical, it does not help patients whose disease has spread, and so we wanted to determine what was causing this to happen."

The researchers analized The Cancer Genome Atlas (TCGA) and identified 41 genes inversely correlated with survival in breast cancer. Huang and colleagues focused on one gene in particular: GABAA receptor alpha3 (Gabra3). The gene was particularly intriguing, since prior to this study, researchers believed that Gabra3 was only found in brain tissue.

There were three main reasons the researchers determined it was worth studying. First, it's highly expressed in cancer tissues, but not in healthy breast tissues. Second, it's a cell surface molecule and therefore

something that could be potentially targeted by a drug. Finally, drugs that target Gabra3 are already available for treating other diseases like insomnia. The researchers showed that cells expressing Gabra3 were better at migrating and invading than their control counterparts, and Gabra3 showed metastasis-promoting activity in vivo, and animal models injected with the activated gene all developed metastatic lesions in their lungs. It does so by activating the AKT pathway, a cellular pathway essential to cell growth and survival in many types of cancer including breast cancer.

In some instances, though, certain types of Gabra3 are actually able to suppress breast cancer metastasis. This is closely linked to the RNA of the gene. RNA is a type of molecule similar to the DNA that encodes our genes, and recent discoveries have shown that RNA has a complex role in regulating how genes are turned on or off. In a phenomenon known as "RNA editing," small changes can be made to RNA nucleotide sequences even after they've been generated.

Huang and colleagues found that Gabra3 that had undergone RNA editing was found only in non-invasive breast cancers. When the RNA is edited, it suppressed the activation of the AKT pathway required for metastasis, meaning that breast cancer with this specific type of Gabra3 was unable to spread to other organs. This is particularly encouraging since signaling proteins called interferons can increase RNA editing activity and could therefore prevent Gabra3 from activating the AKT pathway.

"We believe this is the first time that anyone has demonstrated the importance of RNA editing in breast cancer," Huang said. "A combination strategy that that involves targeting Gabra3 while also upregulating the expression of RNA editing molecules could be an effective strategy for managing metastatic breast cancer."

In addition to further studying the role of Gabra3 in breast cancer metastasis, Wistar is actively seeking collaborative development partners to advance the targeted use of existing GABA-A receptor antagonists in Gabra3 overexpressing tumors. Furthermore, Wistar is interested in collaborations to develop blood-brain barrier impermeable GABA-A receptor antagonists as next generation oncology therapeutics.

**More information:** *Nature Communications*, dx.doi.org/10.1038/ncomms10715

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