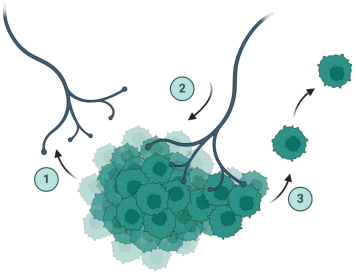
Breast Cancer May Spread by Recruiting Nearby Sensory Nerves

September 20, 2024, by Sharon Reynolds

The body is packed with sensory nerves that pass sensations like touch, pain, and temperature to the nervous system. Such nerves are tangled through tissues in every organ and many tumors. And according to a new study, breast tumors have an unusual way of exploiting these nerves to help them spread to other parts of the body.



A new study shows how cells in breast tumors (1) recruit nearby nerves to (2) move into the tumors and (3) help the cancer spread to other parts of the body.
Credit: Created by Nadia Jaber with Biorender.com

Previous research has found that direct contact between cancer cells and certain kinds of nerve cells can fuel tumor growth. Scientists have even observed some types of cancer cells crawling along nerves to spread (metastasize), explained the study's lead investigator, Veena Padmanaban, Ph.D., a postdoctoral researcher at Rockefeller University.

Although the research team's work implicated sensory nerves as a critical contributor to breast cancer metastasis, they found that breast cancer cells use them in an entirely different way. The team identified a complex process that starts with blood vessels within tumors releasing a molecule that draws nerves closer to them. The biological changes initiated by this close proximity eventually leads to the activation of

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metastasis-fueling genes in the cancer cells.

“This is a contact-independent mechanism. Cancer cells don’t have to be touching the nerves for this [communication] to happen,” Dr. Padmanaban explained.

The findings were published August 7 in *Nature*.

The discovery of this process provides an opportunity for developing treatments that stop it, the study team believes, and potentially prevent breast cancer from spreading. In fact, in the study, they showed that a drug used to prevent nausea and vomiting caused by chemotherapy can block one of the steps of the nerve–cancer cell interaction and stop tumor growth and metastasis in mouse models of breast cancer.

Harnessing the nervous system to fuel tumor growth

Over the last decade, researchers have begun to uncover the intricate processes by which the nervous system helps tumors grow and spread. The fact that the nervous system appears to contribute to tumor growth isn’t necessarily surprising, said Brunilde Gril, Ph.D., of NCI's Division of Cancer Biology, who was not involved in the study.

“The nervous system is involved in many physiological functions of the body,” Dr. Gril said. For example, nerves support the development of organs and regulate functions of epithelial cells, which are the most abundant cells in the body and give rise to most breast cancers, she explained.

Previous research from the lab of the study’s senior investigator, Sohail Tavazoie, M.D., Ph.D., found that blood vessels in breast tumors that had spread in the body express a protein called SLIT2, which is known to play a role in directing where nerves grow in the body.

In their new study, funded in part by NCI, Dr. Padmanaban and her colleagues from the Tavazoie lab wanted to see if nerves within the tumor microenvironment interacted with breast cancer cells and whether they helped drive tumor

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growth and spread.

In a series of experiments, they found that blood vessels within tumors had to express SLIT2 to draw in sensory nerves. For example, when they transplanted human breast cancer cells into mice and deleted SLIT2 from endothelial cells, the resulting tumors lost their ability to attract sensory nerves.

Looking at tumor samples collected from people with breast cancer, the team found that people whose breast tumors had a greater abundance of sensory nerves were more likely to have their cancers metastasize. They observed a similar effect in mice implanted with breast cancer cells.

Fueling metastasis from a distance

In these experiments, although the sensory nerves appeared to be fueling tumor growth and spread, the two cell types weren't physically touching, the researchers found. So how were the nerves exerting their effect?

By analyzing and testing substances secreted by both the nerves and the breast cancer cells, the researchers found that a tiny protein called substance P released by sensory nerves substantially boosted growth and spread of breast cancer cells growing in laboratory dishes. Large amounts of substance P were found in samples of human breast tumors that had spread to the lymph nodes.

In mice with breast tumors, blocking substance P greatly reduced tumor growth and metastasis.

But how exactly was substance P promoting metastasis? Dr. Padmanaban and her colleagues found that substance P induces its effects by binding to a receptor on tumor cells called TACR1.

Surprisingly, when this binding occurred, the end result was death for the small subset of breast tumor cells that expressed high levels of the receptor.

When these cells died, they released a type of genetic material

called ssRNA, which is normally a signal to the body that a viral infection has occurred.

This ssRNA switched on another receptor found on cancer cells, called TLR7. While TLR7 is involved in the body's normal immune response, numerous studies have shown that it can also help tumor cells spread.

In this scenario, metastasis "appears to be dependent on a small but significant number of cancer cells dying," Dr. Tavazoie explained. "But by dying, they're helping the rest of the cancer cells in the tumor proliferate and metastasize."

Can this metastatic process be stopped?

With so many pieces having to fit into place for this process to work, the researchers wondered whether—like pulling out the wrong piece in a Jenga tower—disrupting just one could cause the whole cycle to break down.

Aprepitant, sold under the brand names of Cinvanti and Emend in the United States, is approved to help treat nausea and vomiting caused by some cancer treatments. It works by blocking TACR1, one of the first molecules involved in this newly discovered metastatic process.

In several mouse models of metastatic breast cancer, tumor growth slowed when the researchers treated the mice with aprepitant. And in other mouse models, those that got the drug were much less likely to develop metastases than those that didn't.

Although aprepitant is an approved drug, it has never been tested in people for potential effects on tumor progression and metastasis, Dr. Gril explained. But the promising results of the experiments in mice suggest that more research to evaluate its potential long-term use and interactions with other cancer treatments are warranted, she added.

The idea of using aprepitant as part of cancer treatment "adds to a bigger conversation that's been going on about

repurposing drugs for cancer," Dr. Padmanaban said. For example, other researchers recently found that beta blockers prescribed to treat high blood pressure may have an antimetastatic effect. Clinical trials are now testing this idea.

It's not yet clear how early the communication between sensory nerves and cancer cells starts during breast tumor formation, or if other types of cells in the body, such as immune cells, may also play a role in this process, Dr. Padmanaban said, adding "there's so much more work to be done."

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