

Instead of Fighting Breast Cancer, Immune Cell Promotes Its Spread

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Researchers at the UC San Diego School of Medicine and the Moores UCSD Cancer Center have new evidence that a type of immune system cell thought to be part of the first line of defense against breast cancer may also help promote its spread. They have found that when these cells, known as lymphocytes, make an inflammatory protein called RANKL (RANK ligand), breast cancer is more likely to spread to the lungs.

They have also shown that blocking a cascade of cellular signals that follow RANKL's docking to its receptor (RANK) on tumor cells can halt cancer progression, or metastasis, and may be a possible target for drug therapy.

The scientists, led by first author Wei Tan, PhD, a postdoctoral fellow in the Department of Pharmacology at the UC San Diego School of Medicine and Michael Karin, PhD, professor of pharmacology in UCSD's Laboratory of Gene Regulation and Signal Transduction, say that the findings establish RANKL as a potential marker that can be used to help determine breast cancer prognosis and adds further proof to the potentially important role of inflammation in cancer development and spread. They reported their findings April 22, 2009 at the AACR 100th Annual Meeting 2009 in Denver.

According to Tan, the role of lymphocytes in breast cancer progression has been controversial for the last 20 years. Such cells are supposed to detect and eliminate cancer cells, but paradoxically, the infiltration of lymphocytes such as B cells and T cells into breast cancer is sometimes an indicator of poor prognosis, including cancer recurrence and metastasis. RANKL has been shown in previous studies to be an important inflammatory protein that can lead to bone loss by activating cells that help break down bone. Along with another protein, IKK alpha, it has been implicated both in tumor formation and metastasis.

The researchers created two types of mice that developed breast tumors. One group had lymphocytes in the tumors and expressed RANKL while the other group did not. They found that the group lacking RANKL had significantly fewer lung metastases than those mice with RANKL. They then took tumor cells from both types of mice and injected them into mice with the same genetic background to avoid rejection and monitored the ability of the mice to form tumors and metastases to the lung.

The researchers didn't find any lung tumor metastases in mice without lymphocytes. Yet, when RANKL was injected into the animals, the same potential for the cancer to spread was restored, indicating that the lymphocytes, which make RANKL, are critically important to the process.

"Without lymphocytes, there is no metastasis," said Tan. "If we treat the mice with RANK ligand, there are metastases, which indicate that RANK ligand can compensate for the function of lymphocytes."

The study establishes the role of RANKL-expressing lymphocytes as a promoting factor in breast cancer metastasis and provides a potentially good marker for breast cancer prognosis, the researchers said.

Tan noted that additional experiments showed that blocking both RANKL and IKK alpha in those breast tumor cells inhibited lung metastases. "More importantly," he said, "blocking the signaling pathway downstream of RANKL blocks primary metastasis and can potentially be developed as a treatment strategy."

Results such as these are helping to change the thinking about inflammation and cancer. "In general, we used to think that inflammation in the immune response is a part of the host defense against the tumor, but now we think that there are different kinds of inflammation," Tan said. "For example, T-helper cells can activate an anticancer response, but can also promote a separate tumor promoting response. In this study, if we target the host pro-tumor inflammation and immune response, we can also reduce tumor metastasis and are very likely to develop a therapy that is more effective."

The research received funding support from Susan G. Komen for the Cure.

Other co-authors include: Weizhou Zhang, Amy Strasner, UCSD Department of Pharmacology; Robert Hoffman, AntiCancer, Inc.; and William Dougall, Amgen Inc, Seattle.

The Moores UCSD Cancer Center is one of the nation's 41 National Cancer Institute-designated Comprehensive Cancer Centers, combining research, clinical care and community outreach to advance the prevention, treatment and cure of cancer. For more information, visit <http://health.ucsd.edu/cancer>

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