Researchers Learn How Signaling Molecule Orchestrates Breast Cancer's Spread

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A study led by researchers at Memorial Sloan Kettering Cancer Center (MSKCC) has uncovered how breast tumors use a particular type of molecule to promote metastasis - the spread of cancer cells. Metastasis is the cause of approximately 90 percent of all cancer-related deaths. The study is published in the April 4, 2008, issue of *Cell*. [PubMed Abstract]

> Our work reveals how tumor cells learn to exploit cytokines…to promote the spread of breast cancer.
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> Joan Massagué, PhD, study's senior author and Chairman of the Cancer Biology and Genetics Program at MSKCC and a Howard Hughes Medical Institute investigator

The work examines how cells in the body communicate with each other through cytokines, signaling molecules that direct a wide range of activities such as cell growth and movement. One important cytokine - transforming growth factor β (TGF β) - normally suppresses tumor development. However, according to the findings, cancer cells in humans are able to misuse these cytokines for their own gain by compelling TGFβ to enhance a tumor's ability to spread instead of suppressing it.

Using computer-based analysis to classify patient tumor samples based on their levels of TGFβ , the researchers observed that about half of all breast tumors contained active TGFβ . The affected tumors were found to be more aggressive and more likely to metastasize to the lung during the course of the patients' disease.

Using mice for their next set of experiments, the researchers discovered that TGFβ prompts breast cancer cells to make a second cytokine, known as angiopoietin-like 4 (ANGPTL4), which enhances the ability of the cancer to spread to the lungs through the blood circulation. The results show that the breast cancer cells use ANGPTL4 to break down the thin capillaries of the lung, thus facilitating their escape into the lung tissue.

"Our work shows that TGFβ enhances human breast cancer metastasis and reveals how tumor cells learn to exploit cytokines by making them work as a relay system to promote the spread of breast cancer," said the study's senior author, Joan Massagué, PhD , Chairman of the Cancer Biology and Genetics Program at MSKCC and a Howard Hughes Medical Institute investigator.

The researchers are now seeking to determine whether TGF and ANGPTL4 may also be active in other types of tumors, and are evaluating ways to interfere with the action of these cytokines to prevent metastasis in cancer patients.

"Deciphering how cancer cells take advantage of these cytokines is essential for developing therapies that can prevent this process," said the study's lead author David Padua, a graduate student in Dr. Massagué's lab. "Because cytokines act outside of cells they can be more easily targeted by drugs that block their activity."

The study provides support for developing agents to interfere with TGFβ in order to prevent and treat cancer metastasis. It points at ANGPTL4 as a possible target to interrupt the TGFβ stimulus of metastasis without interfering with the molecule's beneficial effects. Several pharmaceutical companies are currently testing TGFβ -blocking compounds in clinical trials as candidate drugs against breast cancer, melanoma , and other types of cancer.

This work was co-authored by Xiang H-F. Zhang and Qiongqing Wang of MSKCC's Cancer Biology and Genetics Program, and William L. Gerald, MD,

PhD, a surgical pathologist and member of the Human Oncology and Pathogenesis Program at MSKCC. Cristina Nadal, PhD, of the Hospital Clínic-IDIBAPS and Roger R. Gomis, PhD , of the Institute for Research in Biomedicine (IRB Barcelona), both of Barcelona, Spain, also contributed to this research.

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