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'Microtentacles' on tumor cells appear to play role in how breast cancer spreads

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University of Maryland Medical Center
Summary:
Researchers have discovered that "microtentacles," or extensions of the plasma membrane of breast cancer cells, appear to play a key role in how cancers spread to distant locations in the body. Targeting these microtentacles, which are linked to a protein called "tau," might prove to be a new way to prevent or slow the growth of these secondary cancers, the scientists say.

Researchers at the University of Maryland Marlene and Stewart Greenebaum Cancer Center have discovered that "microtentacles," or extensions of the plasma membrane of breast cancer cells, appear to play a key role in how cancers spread to distant locations in the body. Targeting these microtentacles might prove to be a new way to prevent or slow the growth of these secondary cancers, the scientists say.

They report in an article to be published online March 15, 2010, in the journal *Oncogene* that a protein called "tau" promotes the formation of these microtentacles on breast tumor cells which break away from primary cancers and circulate in the bloodstream. While twisted remnants of tau protein have been seen in the brain tissue of patients with Alzheimer's disease, this is the first report that tau could play a role in tumor metastasis by changing the shape of cancer cells. These tau-induced microtentacles can help the cells reattach to the walls of small blood vessels to create new pockets of cancer.

"Our study demonstrates that tau promotes the creation of microtentacles in breast tumor cells. These microtentacles increase the ability of circulating breast tumor cells to reattach in the small capillaries of the lung, where they can survive until they can seed new cancers," says the senior author, Stuart S. Martin, Ph.D., a researcher at the University of Maryland Greenebaum Cancer Center and associate professor of physiology at the University of Maryland School of Medicine. Michael A. Matrone, Ph.D., is the study's lead author.

Healthy cells are programmed to die -- a process called apoptosis -- after they break off of epithelial layers that cover internal organs in the body. They also can be crushed if they are forced through small capillaries. However, cancer cells are able to survive for weeks, months and even years in the body. Once they are trapped in small blood vessels, the cells can squeeze through microscopic gaps in the vessels' lining and spread to organs such as the brain, lung and liver.

"We hope that through our research, we will be able to identify drugs that will target the growth of these microtentacles and help to stop the spread of the original cancer. Drugs that reduce tau expression may hold potential to inhibit tumor metastasis," Dr. Martin says.

He notes that metastatic cancers are the leading cause of death in people with cancer, but methods used to treat primary tumors have limited success in treating metastatic cancer. In breast cancer, metastases can develop years after primary tumors are first discovered.

Tau is present in a subset of chemotherapy-resistant breast cancers and is also associated with poor prognosis, but Dr. Martin adds, "While tau expression has been studied in breast cancers for contributing to chemotherapy resistance, the protein's role in tumor cells circulating in the bloodstream hasn't been investigated. And that's the focus of our research."

In this recent study, the University of Maryland researchers analyzed breast tumor cells from 102 patients and found that 52 percent had tau in their metastatic tumors and 26 percent (27 patients) showed a significant increase in tau as their cancer progressed. Twenty-two of these patients even had tau in metastatic tumors despite having none in their primary tumors.

Dr. Martin says more studies are needed to determine if tau is a clear predictor of metastasis. Given the complex nature of tumors, there most likely are other factors involved in causing cancers to spread, he says.

"Metastasis is a very major concern for people diagnosed with cancer, and the discovery of these microtentacles and the role that tau plays in their formation is a very exciting development that holds great promise for developing new drugs," says E. Albert Reece, M.D., Ph.D., M.B.A., acting president of the University of Maryland, Baltimore, and dean of the University of Maryland School of Medicine.

The University of Maryland, Baltimore, has filed patents on the microtentacle discoveries of Dr. Martin's lab group and is looking to partner with biopharmaceutical companies on new drug development. The researchers identified these cell extensions while they were studying the effects of two drugs that prevent cell division, or mitosis. Most chemotherapy drugs target cell division, aiming to slow or stop tumor growth.

Dr. Martin says his team found that a popular chemotherapy drug, taxol, actually causes cancer cell microtentacles to grow longer and allows tumor cells to reattach faster, which may have important treatment implications for breast cancer patients. Their studies are continuing.

"We think more research is needed into how chemotherapies that slow down cell division affect metastasis. The timing of giving these drugs can be particularly important. If you treat people with taxol before surgery to shrink the primary tumor, levels of circulating tumor cells go up 1,000 to 10,000 fold, potentially increasing metastasis," he adds.

The study being published in Oncogene was funded by grants from the National Cancer Institute, the USA Medical Research and Materiel Command, and the Flight Attendants Medical Research Institute.