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Scientists identify protein key to breast cancer spread, potential new drug target

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Researchers at the Kimmel Cancer Center at Jefferson have identified a protein that they say is key to helping a quarter of all breast cancers spread. The finding, reported online the week of April 9, 2007 in the journal *Proceedings of the National Academy of Sciences*, could be a potential target for new drugs aimed at stopping or slowing the growth and progression of breast cancer.

Kimmel Cancer Center director Richard Pestell, M.D., Ph.D., professor and chair of cancer biology at Jefferson Medical College of Thomas Jefferson University in Philadelphia, and colleagues genetically engineered mice to lack the protein Akt1, which normally plays a role in keeping cells alive by interfering with programmed cell death. Breast and other cancers make an overabundance of the protein, and it's thought to potentially affect survival of breast and other cancer cells as well.

To test that hypothesis, Dr. Pestell and his team bred the mice missing the gene for Akt1 with other mice that overexpressed the HER2-neu (ErbB2) oncogene, which leads to approximately 25 percent of all breast cancers. They then examined the role of Akt in the onset and progression of breast cancer in the resulting offspring.

To their surprise, mice lacking two copies of the gene that produces Akt1 rarely had any tumors. Those mice that carried only one copy of the Akt1 gene developed some tumors, but they were small and developed more slowly. Mice with two copies of Akt1 rapidly developed significant cancer.

“The finding was exciting because it told us that Akt1 is a potentially useful target for ErbB2-positive breast cancer,” Dr. Pestell says. “More interesting was that even if the mouse developed a tumor, it didn’t develop metastases. We proved that there was a requirement for Akt1 in metastasis, which makes Akt1 an exciting target for metastatic breast cancer. We knew that Akt1 could play a role in cell growth and size, but the idea that it could play a role in migration and metastasis was an unexpected new finding,”

The researchers also proved how, showing that Akt1 causes the cancer cells to secrete a factor – CXCL16 – that promotes breast cancer cell migration. Without Akt, cancer cells failed to migrate. They also showed that deleting Akt1 completely blocked breast cancer metastasis to the lungs, while mice that expressed Akt1 died from lung metastasis.

While scientists have looked at Akt as a drug target, notes Arthur Pardee, Ph.D., professor emeritus of medical oncology at the Dana-Farber Cancer Institute in Boston, its role in metastasis is less emphasized. “Blocking this with anti-Akt drugs might provide a novel treatment, especially against early cancers,” he says.

While the monoclonal antibody drug Herceptin has been very successful in treating ErbB2-positive breast cancer, patients can relapse, Dr. Pestell notes, and other drug targets are needed. The newly found secreted factor may prove to be such a target.

Source: Thomas Jefferson University