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Researchers show antibody to breast cancer-secreted protein blocks metastasis

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Scientists at the Kimmel Cancer Center at Thomas Jefferson University in Philadelphia have made a key discovery about the mechanism of breast cancer metastasis, the process by which cancer spreads. Focusing on a gene dubbed "Dachshund," or DACH1, they are beginning to pinpoint new therapeutic targets to halt the spread of cancer.

Reporting their findings in the *Proceedings of the National Academy of Sciences*, researchers led by Richard Pestell, M.D., Ph.D., director of the Kimmel Cancer Center at Jefferson and professor and chair of Cancer Biology at Jefferson Medical College, showed that breast cancer cells secrete a common inflammatory protein, IL-8. When the scientists blocked the protein in mice with an antibody, they found that it completely halted the spread of breast cancer to the lungs.

In addition, the team found that the DACH1 gene normally blocks the production of IL-8.

"This is a very important study by Dr. Pestell and his colleagues that demonstrates that the protein dachshund blocks metastasis in a mouse model and that this occurs through reduced production of the chemokine IL-8," says Max Wicha, M.D., director of the University of Michigan Comprehensive Cancer Center in Ann Arbor. "Interestingly reduced dachshund and increased IL-8 are associated with aggressive metastatic breast cancer in women. Our laboratory has found that IL-8 regulates breast cancer stem cells and that these cells mediate metastasis. Dr Pestell's work suggests that dachshund is a key regulator of this process."

DACH1 normally regulates eye development and development of other tissues, playing a role in determining the fate of some types of cells. In previous work, Dr. Pestell and his co-workers showed that DACH1 can commandeer cancer-causing genes and return them to normal. The team found evidence from more than 2,000 breast cancer patients that the more the gene is expressed in breast cancer, the better the patient did, enabling it to predict an individual's prognosis.

Because the researchers knew that DACH1 is lost in such invasive breast cancers that carry poor prognoses, they investigated its potential role in the cancer cells' ability to migrate and invade, the prelude to metastasis. They focused on its effects on cancer-causing oncogenes, such as Ras and Myc.

In a series of experiments, the scientists, led by Dr. Pestell and first author Kongming Wu, Ph.D., assistant professor of Cancer Biology at Jefferson Medical College, looked at the effects of adding DACH1 to breast cells made cancerous by various oncogenes. When they added DACH1 to Ras-induced breast cancer cells, for example, they saw a greater than 75 percent reduction in cell migration. Cells turned cancerous by the oncogene ErbB2 showed a 50 percent drop in migration. Cells made cancerous by Myc also had 50 percent less migration.

The researchers performed a proteomic analysis, testing the expression of many proteins at once to see which might be regulated by DACH1. They found that IL-8 is a critical target of DACH1 that helps regulate breast cancer cell migration and metastasis. In mouse studies, they showed that DACH1 lowered the levels of IL-8 genetic material (mRNA) by approximately 90 percent in cancers caused by Ras.

According to Dr. Wu, the gene for IL-8 is also a known target of Ras, helping recruit the formation of new blood vessels to feed a developing

cancer – a process called angiogenesis. He notes that it's well known that tumors with high levels of IL-8 have a poorer clinical prognosis.

"The findings suggest an important role for IL-8 in blocking the progression of cancer and metastasis," says Dr. Wu. "Because IL-8 is a commonly found protein, it's possible to use this to block metastasis, perhaps eventually as a target for gene therapy."

Source: Thomas Jefferson University