'Bridge' protein spurs deadliest stages of breast cancer

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A protein known for its ability to "bridge" interactions between other cellular proteins may spur metastasis in breast cancer, the disease's deadliest stage, a study from Burnham Institute for Medical Research has found.

Led by professor Gen-Sheng Feng, Ph.D., and colleagues at Burnham and Royal Victoria Hospital in Montreal, Quebec, the study ranks among the first to more precisely define the cancer role for the protein known as Gab-2. These results, to be published in the journal *Oncogene*, have been made available to the worldwide medical research community by priority posting online at the journal's website.

The protein has been of keen research interest for its role in breast cancer, but whether it controlled metastasis or initial tumor growth was unknown. Gab-2 is one of a group of proteins known as "scaffold" or "bridge" proteins, which provide a molecular intermediary to help cell signal proteins interact.

"Although Gab-2 is highly expressed in breast cancer, it is not essential for the development of cancer," said Feng. "We found that Gab-2 is, however, essential for metastasis, or the spread of cancer. Breast cancer victims can survive before metastasis, but their chances decrease significantly when the cancer cells have spread. If we can understand precisely how Gab-2 functions in metastasis, then we might be able use this knowledge to design treatments that would block the deadly metastasis."

Feng, who studies molecular signaling in embryonic stem cells and examines signaling pathways that are involved in obesity and diabetes, has studied the roles played by Gab-2 and its chemical cousin Gab-1, in various disorders. His fundamental analyses of cell signaling for Gab-2 led him to study the protein in cancer cells.

Feng and his colleagues began by examining Gab-2's role in a pathway influenced by the cancer-causing oncogene Neu, which is implicated in nearly 30 percent of human breast cancers and associated with poor survival rates. While scientists have known that the Neu pathway drives cancer development and metastasis (and can be treated with the drug Herceptin with a certain degree of success), the molecular mechanisms that lead to breast cancer development and metastasis are not fully understood.

Feng worked with mice a special strain of mice which lacks the gene for Gab-2. The Gab-2 mutant mice were bred with two types of mice; one with an active gene that induced metastatic breast cancer tumors and another that grew breast cancer cells with low potential for metastasis.

The mutant mice showed minor effects from the initial growth of breast cancer cells, Feng and his team found, indicating that Gab-2 has little effect on inducing cancer cell growth. However, in the mice pre-disposed to metastatic breast caner, the lack of Gab-2 potently reduced metastasis rates, indicating that Gab-2 was necessary for metastasis, if not for initial tumor growth.

Since Gab-2 is a scaffold molecule and is possibly part of many signaling pathways, Feng's group wanted to determine how it influences cancer cell growth. They studied pathways known as Akt and Erk, well-known parts of the Neu oncogene pathway, in the mice lacking Gab-2 and found that while levels of Akt signals were unaffected by Gab-2's absence, Erk signals were significantly reduced.

"It appears that Akt and Erk pathways have distinctive roles in mammary tumors; initiation and growth for Akt and metastasis for Erk," said Feng. "We suspect that Gab-2 might promote mammary cell metastasis through Erk activation. This is a novel mechanism for breast cancer metastasis which makes Gab-2 a possible new target for the design of therapies for metastatic breast cancer."

Feng and his team are now looking at the other molecules that assist the scaffold protein Gab-2's effects on breast cancer metastasis.

Source: Burnham Institute