Medical Xpress

Researchers discover novel role of the NEDD9 gene in early stages of breast cancer

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Breast cancer is the second leading cause of cancer deaths among women in the United States. Many of these deaths occur when there is an initial diagnosis of invasive or metastatic disease. A protein called NEDD9—which regulates cell migration, division and survival—has been linked to tumor invasion and metastasis in a variety of cancers. Researchers at Fox Chase Cancer Center have now shown that NEDD9 plays a surprising role in the early stages of breast tumor development by controlling the growth of progenitor cells that give rise to tumors. The findings, published in the journal *Oncogene* on January 14, 2013, could lead to personalized treatment strategies for women with breast cancer based on the levels of NEDD9 in their tumors.

"For several years, NEDD9 has been linked to tumor metastasis and invasion at later stages. This is the first study that really shows how important NEDD9 can be for the initiation of tumors in breast cancer, and to link this initiation process to progenitor cells," says lead study author Joy Little, PhD, a postdoctoral fellow at Fox Chase who works in the laboratory of senior study investigator Erica A. Golemis, PhD, Deputy Chief Scientific Officer and Vice President at Fox Chase.

In the study, Little, Golemis and their collaborators mated mice without the NEDD9 gene to mice engineered to develop HER2+ mammary tumors and unexpectedly found that these mice were largely resistant to tumor formation. Only 18% of the mice developed mammary tumors, compared with 80% of mice that had a functional NEDD9 gene. In contrast to previous research findings showing that an increase in

NEDD9 levels promotes tumor aggressiveness, the researchers found that loss of NEDD9 had little effect on tumor metastasis, indicating that it is not required for this process in this specific context. Once formed, the tumors in mice lacking NEDD9 grew rapidly, suggesting that it either plays a less important role at later stages of tumor growth or tumors undergo compensatory changes that allow them to bypass the need for NEDD9.

Importantly, mice lacking NEDD9 showed a significant reduction in progenitor cell populations in the mammary gland compared with mice that had a functional NEDD9 gene. Progenitor cells from NEDD9-null mice were less likely to form three-dimensional mammospheres in culture, but proliferated at the same rate as cells from control mice. The loss of Nedd9 also made progenitor cells more sensitive to lower doses of two tumor-inhibiting drugs—a Food and Drug Administration-approved Src inhibitor called dasatinib, and a focal adhesion kinase inhibitor from a class of drugs currently being tested in clinical trials for the treatment of cancer. These findings suggest that these types of drugs would more effectively control breast cancer tumors with low levels of NEDD9.

"Eventually, with a biopsy, you may be able to get a read-out of all the mutations that a tumor has, and each one would potentially dictate whether or not a certain line of therapy would work for a specific tumor," Little says. "If NEDD9 levels are higher in a particular tumor, we could potentially determine whether or not it would be more sensitive to specific inhibitors."

To follow up on this work, the researchers plan to determine the mechanisms by which NEDD9 controls tumor formation, and examine whether NEDD9 plays a similar role in early stages of other types of cancer.