Team identifies new breast cancer tumor suppressor and how it works

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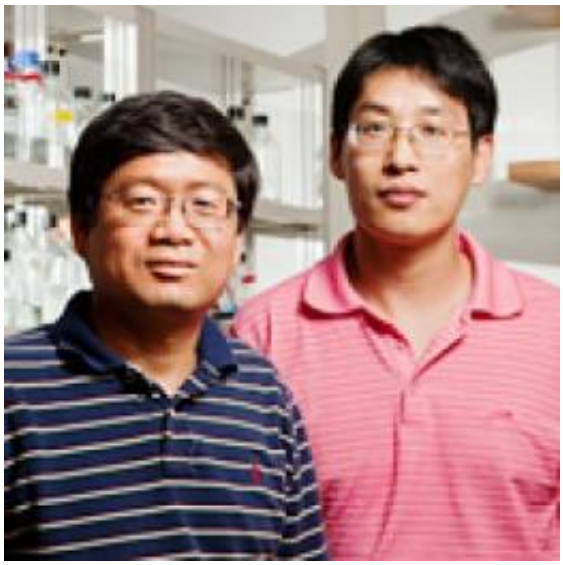

University of Illinois medical biochemistry professor Lin-Feng Chen (left), research scientist Bo Huang and their colleagues identified a new breast cancer tumor suppressor protein, Runx3, and determined how it functioned. Credit: L. Brian Stauffer

Researchers have identified a protein long known to regulate gene expression as a potent suppressor of breast cancer growth. Their study, in the journal *Oncogene*, is the first to demonstrate how this protein, known as Runx3, accomplishes this feat.

"People suggested that Runx3 might be a tumor suppressor in breast cancer because they found that it is down-regulated in a lot of breast cancer cell lines and breast cancer tissues," said University of Illinois medical biochemistry professor Lin-Feng Chen, who led the study. But no previous studies uncovered direct evidence to support that idea, he said.

In the new study, Chen and his colleagues at Nagasaki University discovered that a significant proportion of mice lacking one of two Runx3 genes spontaneously developed mammary gland tumors at 14 or 15 months of life - an age corresponding to age 40 to 50 in humans.

"We found mammary tumors growing in about 20 percent of the female mice lacking a copy of the Runx3 gene," Chen said. None of the mice with two normal copies of the gene developed tumors.

The researchers also found that estrogen receptor alpha (ER-alpha), a well-known culprit in the development of many breast tumors, was up-regulated in the mouse tumors. ER-alpha is overexpressed in about 75 percent of human cases of breast cancer, and enhanced ER-alpha expression in normal breast tissue is associated with an increased risk of breast cancer, Chen said.

Circulating estrogen binds to ER-alpha and initiates a chain of events that alter gene expression in the targeted cell. This is a normal part of cellular signaling, but in ER-positive breast cancers, the overexpression of ER-alpha leads to enhanced tumor cell survival, growth and proliferation.

The researchers found that when Runx3 was re-introduced into ER-alpha positive breast cancer cell lines, it suppressed the growth of the cancer cells and inhibited the potential of the cancer cells to form tumors in the mouse. Further experiments revealed that Runx3 actually targeted ER-alpha signaling by inducing the degradation of ER-alpha.

"By regulating the cellular levels of ER-alpha, Runx3 appears to control the cell's response to circulating estrogen, thus playing an important role in the onset of breast cancer," Chen said.

Chen sees three potential benefits that spring from this study. First, the researchers have discovered a mouse model of spontaneously occurring mammary tumors that corresponds to an age of increased risk of breast cancer in humans.

Second, Chen hopes to develop a simple test to measure Runx3 levels in mammary tissue.

"We know from other people's studies that Runx3 is inactivated in the early stages of breast cancer," he said. "So we might be able to use Runx3 as a biomarker of early stage breast cancer."

And third, since the Runx3 gene appears to be intact but inactivated in breast cancer, future studies will focus on reversing its inactivation, Chen said.

"If you can reactivate Runx3, then you can suppress tumor growth," he said.

The study team also included researchers from the University of Pittsburgh Medical Center and the National University of Singapore.

More information: "RUNX3 Acts as a Tumor Suppressor in Breast Cancer by Targeting Estrogen Receptor Alpha," *Oncogene* (2011)

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