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Protein disables p53, drives breast cells toward cancer transition

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The recently identified TRIM24 protein plays an active role in pushing normal breast cells into rapid cell proliferation and, potentially, into breast cancer.

Reporting in the journal *Nature*, a team led by researchers at The University of Texas MD Anderson Cancer Center found that TRIM24 (tripartite motif-containing 24) pushes estrogen-responsive genes toward active expression. This expression, in turn, sets the stage for malignant transformation of breast cells. TRIM24 functions by reading a specific code, or signature, present at estrogen-regulated genes and recruiting estrogen receptors for gene activation. About 70 percent of breast cancers are estrogen receptor positive; their growth is driven by the hormone estrogen.

Tumor-suppressor labeled for destruction

TRIM24 is a chromatin regulator that normally maintains the tumor suppressor p53 at low levels until it is summoned to reduce cellular stress or DNA damage in cells. Abnormally high expression of TRIM24, however, suppresses p53 levels, making cells more vulnerable to the types of cellular damage that lead to cancer. In breast cells, high levels of TRIM24 also stimulate estrogen receptor activity, delivering a one-two punch that fuels cell proliferation and growth.

"We found that TRIM24 negatively regulates p53 by placing ubiquitin

on it and thereby labeling it for destruction," said Michelle C. Barton, Ph.D., professor in the Department of Biochemistry and Molecular Biology at MD Anderson. "Two of TRIM24's structural domains indicated that it probably interacts with proteins called histones that spool DNA into chromatin. TRIM24 is an interpreter of specific modifications placed on histones that function like a barcode - we call this the histone code or histone barcode." TRIM24 then reads the particular barcode that the histone modifications spell out, receiving its instructions on such things as whether to activate a gene.

Barton added that these structural domains suggest that TRIM24 not only can read the histone code but is actually reading a very unusual alphabet spelling of the histone barcode. This unusual histone signature appears at estrogen-response elements-places in the DNA where estrogen receptors bind - and it is regulating estrogen-regulated genes that become overstimulated by TRIM24. These genes push cells into proliferation and probably into tumorigenesis.

Overexpressed TRIM24 cuts survival

When the researchers examined a number of breast cancer cell lines, they found that TRIM24 was overexpressed in each one. "Because TRIM24 is basically undetectable in normal cells," Barton said, "we believe that by virtue of its being overexpressed, it's negatively regulating p53 and overstimulating estrogen receptors that, in turn, promote the proliferation."

Collaboration with MD Anderson's Mien-Chie Hung, Ph.D., chair of the Department of Molecular and Cellular Oncology, further strengthened the case for TRIM24's role in breast cell proliferation and tumorigenesis. When pathologist Weiya Xia, M.D., screened biopsies of 128 breast cancer patients, she found that TRIM24 was overexpressed in 70 percent. These patients had a median overall survival rate of 50 months,

meaning half of them survived at least to that point.

In 30 percent of the women, TRIM24 was either undetectable or expressed at very low levels. In these two groups, the women's breast cancer was non-metastatic, and 90 percent survived to 50 months.

Avenues of future research

"We propose that TRIM24 would be a great therapeutic target - the reason being that if you were to eliminate or inactivate TRIM24, you could potentially restart p53 function and decrease estrogen receptor function in breast tumor cells," Barton said. "In the case of ER-negative tumors, you might still have a chance to go for the p53, and in the case of breast cancers that are p53-negative you might still be able to go for the estrogen receptor."

"We're claiming that TRIM24 promotes tumor development," Barton continued, "and now we're trying to actually prove that by using mouse models in which we overexpress TRIM24 in mammary epithelium cells."

Provided by University of Texas M. D. Anderson Cancer Center