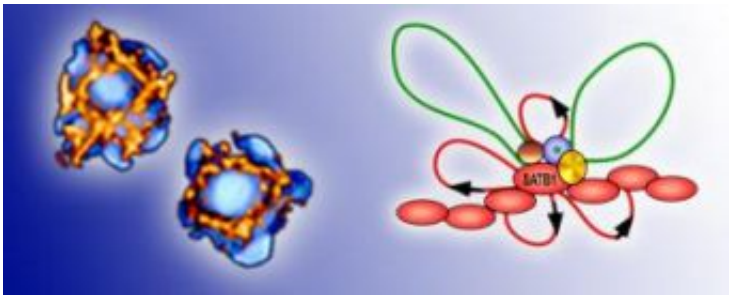
A protein that triggers aggressive breast cancer

March 12 2008



SATB1 forms a three-dimensional cage-like structure within the cell nucleus (left) that binds to DNA specific sites within genes, reorganizes chromatin, and recruits enzymes that promote the expression or suppression of genes (right). Credit: Lawrence Berkeley National Laboratory

SATB1 is a nuclear protein well known for its crucial role in regulating gene expression during the differentiation and activation of T cells, making it a key player in the immune system. But SATB1 has now revealed a darker side: it is an essential contributing factor in the most aggressive forms of breast cancer.

Breast cancer cells need SATB1 to become metastatic; metastasis -- the stage when cells break away from the original tumor and spread to other parts of the body -- is the final step of solid tumor progression and is the most common cause of death in cancer patients.

"In breast tumors, SATB1 reprograms the genome to change the expression of hundreds of genes, promoting tumor growth and metastasis," says Terumi Kohwi-Shigematsu, a scientist in the Life Sciences Division of the Department of Energy's Lawrence Berkeley National Laboratory who, with her colleagues, discovered SATB1 and has since investigated its many functions. She says, "SATB1's role in breast cancer is a new paradigm for the way tumors progress."

Kohwi-Shigematsu, working with Berkeley Lab's Hye-Jung Han and Yoshinori Kohwi, and with Jose Russo of the Fox Chase Cancer Center in Philadelphia, found that when SATB1 is detected in a breast tumor, the cancer is highly likely to progress or recur.

Moreover, by introducing SATB1 into otherwise nonmetastatic breast cancer cells, invasive tumors can be induced in mice; conversely, removing SATB1 from metastatic cells not only abolishes metastasis and tumor growth in mice but also returns cells to their normal appearance in vitro. The researchers have published these and other findings in the March 13, 2008 issue of Nature.

How SATB1 works

Kohwi-Shigematsu and Kohwi originally identified a class of DNA sequences they called base-unpairing regions (BURs), a finding that led Kohwi-Shigematsu's group to the discovery of "special AT-rich sequence binding protein 1" (SATB1). SATB1 binds to BURs in double-stranded DNA by recognizing the BURs' distinctive phosphate-backbone structure. BURs contain unusual sequence contexts that readily unzip to expose DNA's individual strands.

As a nuclear architectural protein, SATB1 forms what Kohwi-Shigematsu calls a "3 D chickenwire network" inside the nucleus of the cell. SATB1 anchors chromosomes to its cage-like structure by tethering

the BURs in the target genes, thus serving as a kind of "glue" for these genes. SATB1 folds and remodels the chromatin -- the intertwined DNA and proteins that form chromosomes -- into new shapes, bringing even distant parts of the genome together for coordinated control of gene expression and regulation.

SATB1 also globally regulates histone status in the chromatin by recruiting histone-modifying enzymes to the target-gene loci. Histones are the proteins around which DNA in chromatin is wound like thread on a spool; histone status renders DNA sequences accessible or inaccessible for transcription.

Early on, SATB1's ability to regulate gene expression was identified as critical to T-cell development. Although Kohwi-Shigematsu and her colleagues have found several other cell types that use SATB1 to reshape chromatin and regulate gene expression in a similar way, SATB1 is not expressed in all cells. SATB1 seems particularly important in cells which must change their function -- as do many progenitor cells, including the thymocytes that turn into T cells. And as cancerous cells must do to turn into metastatic cells.

"Hye-Jung Han of our group started by looking at two dozen breast-cell lines, including normal human epithelial cells" -- epithelial cells are the kind that form the linings of hollow glands in the breast -- "and both nonmetastatic and metastatic breast cancer cells," Kohwi-Shigematsu says. "Only the metastatic cells expressed SATB1, with the most aggressive breast cancer cells showing the highest levels of the protein."

The researchers examined over 2,000 human primary breast cancer tissue samples for which clinical follow-up studies were available. The highest levels of SATB1 were in samples from patients whose survival times had been shortest; patients whose tumor samples had no SATB1 expression generally had longer survival times.

The analysis showed that a high level of SATB1 expression by itself is an excellent indicator of poor prognosis -- independent of whether breast cancer cells have already metastasized to the lymph nodes at the time of diagnosis.

SATB1 takes command

The reason why SATB1 is a good prognostic marker is because SATB1 drives breast cancer cells to become invasive, as revealed by both in vitro and in vivo studies.

The researchers performed in vitro studies of highly metastatic cell lines, reducing SATB1 expression through the use of shRNAs, "short-hairpin-interfering" RNAs, that dramatically reduced the invasive capacity of these cells and also reduced their capacity for unattached growth -- a necessity if metastasizing cancer cells are to travel through the blood and lymph vessels.

Other in vitro studies used normal breast epithelial cells, the kind that form the hollow oriented structures called acini, the milk-secreting glands of the breast. Normal cells form similar, well-organized acinar structures in vitro, whereas in highly metastatic epithelial cell lines these structures are disorganized and lack polarity. When SATB1 expression is reduced in the metastatic cell lines, they too form the kind of polarized, uniform acinar structures found in normal mammary epithelial cells.

These in vitro results were confirmed in vivo, in mice. Nine weeks after human aggressive breast cancer cells were injected into the tails of test mice, these cells developed into metastatic nodules (tumors) on the lungs. But when SATB1 expression was reduced or removed from the injected cancer cells, the mice developed fewer or even no nodules, depending on the remaining levels of SATB1. Once SATB1 is greatly reduced, these cells no longer form tumors when injected directly into

breast fat pads.

In vivo studies also established that cancer cells which do not normally express SATB1, and do not normally metastasize, can become aggressive if they are modified to express SATB1. Once SATB1 is expressed, they form large tumors when injected into breast fat pads; they then invade the blood circulatory system and form metastatic tumors in lungs.

The tests of human breast cancer cell lines in mice allowed the researchers to establish that, for these cells, SATB1 is necessary and sufficient for tumor growth and metastatic activity.

"SATB1 is a key player in the metastasis of breast cancer cells, controlling expression of over a thousand genes," says Kohwi-Shigematsu. "It increases the expression of genes that promote tumor growth and reduces the expression of tumor suppressors. Among the regulated genes are numerous growth-factor genes and genes affecting cell adhesion, cell signaling, cell-cycle regulation, and other functions."

Among the important genes regulated by SATB1, the researcher identified many that are already known to play a role in aggressive breast cancers, including the epidermal growth factor gene ERBB2, otherwise known as HER2.

"What we have found is a new model of altered gene regulation during the progression of tumors, which depends on SATB1's reprogramming of the gene expression profile," Kohwi-Shigematsu says. "What results is a new and aggressive cancer phenotype that promotes both tumor growth and metastasis."

The discovery of SATB1's key part in aggressive breast cancer has profound implications for prognosis and for possible new treatments for cancer's most malignant forms. At the same time, the discovery opens a

wide field of fundamental scientific inquiry, beginning with the most basic questions. What determines the particular sets of genes affected by SATB1 in specific tissues" What other factors may work together with SATB1"

"An important question is what turns on SATB1 during breast cancer progression," says Kohwi-Shigematsu. "That's just the beginning of the things we really want to know."

Source: Lawrence Berkeley National Laboratory

Citation: A protein that triggers aggressive breast cancer (2008, March 12) retrieved 9 April 2024 from https://medicalxpress.com/news/2008-03-protein-triggers-aggressive-breast-cancer.html

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