Lack of CHFR gene expression sets stage for breast cancer

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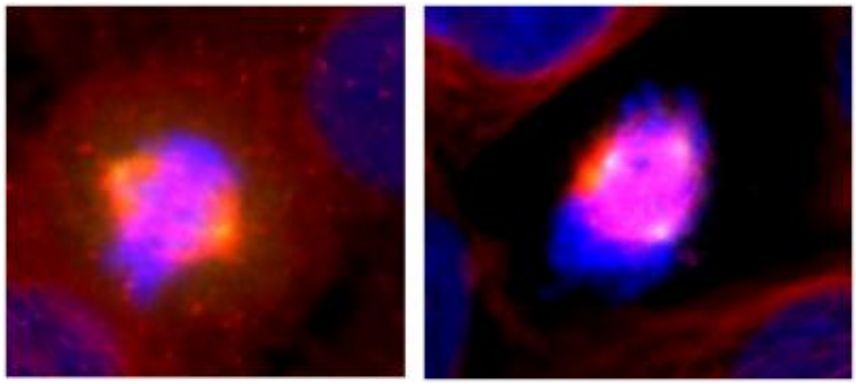

Caption: Left, during normal cell division, a mitotic spindle forms to carry out an orderly division of chromosomes. Right, without expression of the CHFR gene, the mitotic spindle is disorganized and compacted. Credit: Privette et. al., Neoplasia. 2008 July: 10(7):643-652

U-M study lays groundwork for better ways to choose effective treatments, provides insights on other cancers

A University of Michigan study reveals in detail how breast cells produce new cells that are predisposed to become cancerous, unless they receive the protective action of the CHFR gene.

CHFR expression is missing in more than a third of breast cancers. Analysis of this gene is also a hot area of interest among researchers trying to explain colorectal, stomach, lung and other forms of cancer.

The new study reveals how and why new "daughter" cells, produced as cells in body tissues renew themselves, receive too few or too many chromosomes if expression of the CHFR gene is missing or low. The loss of CHFR can lead to the survival of genetically unstable cells loaded with too many chromosomes, which can lead to cancer.

"Our findings show that loss of CHFR disrupts normal chromosome segregation in breast cells during cell division and creates genomic instability, which can drive genetic mechanisms that accelerate the development of cancer," says Elizabeth Petty, M.D., a U-M professor in the departments of human genetics and internal medicine and the senior author of the study. The article appears online ahead of print in the journal *Neoplasia*.

The new knowledge eventually could provide the scientific basis for diagnostic markers and identify which patients can benefit from specific types of cancer drugs.

"Our previous findings, and the work of others, have shown that cancer cells cultured in the lab that have low or absent CHFR expression are more susceptible to treatment with a class of drugs called taxanes, such as paclitaxel (Taxol) and docetaxel, that attack the dividing cells when they are trying to separate their chromosomes," says Lisa Privette, Ph.D., the study's first author, a recent U-M Medical School graduate and now a researcher at Cincinnati Children's Hospital.

"These drugs are frequently used to treat breast cancer and other types of cancer and they work by targeting the structure used to separate chromosomes. Our work provides further evidence for this correlation and begins to explain how the expression of CHFR alters the cell's response to these kinds of drugs."

Why do some women lack CHFR function or have low function in the

first place? Petty says that there's no evidence that women inherit mutations that lead to low or absent CHFR protein.

"It's likely that some other mechanism is shutting down CHFR," she says. "Currently, we are actively looking at ways in which CHFR may be turned off in normal cells, in hopes that we can find a molecular switch to keep it turned on and decrease the risk of cancer development."

Context: The study adds important insights in the continuing search for the roles different genes play in breast cancer. In cell culture studies, Petty's research team previously showed that loss of CHFR was associated with increased tumor size, and that normal breast epithelial cells would develop traits of cancer cells if CHFR was blocked. In the new study, the researchers report what happens inside a dividing cell nucleus when CHFR is missing.

One prime moment in which cancer can begin is when alterations in certain biochemical signals disturb the process by which one cell divides into two. In normal cell division, chromosomes inside the nucleus copy themselves, then line up in the middle of a structure, the mitotic spindle, which forms to aid cell division. The two copies then neatly separate and move to the ends of the spindle, where they become two bundles of identical genetic material. These become the cell's operating instructions for two new daughter cells.

If the spindle doesn't form correctly, genetic material becomes unstable and doesn't divide properly, resulting in cancer-prone cells containing too many chromosomes. The fact that the spindle is affected is important, because some cancer drugs interact with the mitotic spindle as a way to curb cell division.

Research details: Petty and her team studied normal and cancerous human breast tissue samples in cell culture to find out how CHFR

affects certain proteins. They focused on proteins that regulate how spindles form and how chromosomes divide and form along the spindle. The team found that CHFR interacts with alpha tubulin, a protein important in forming mitotic spindles, and with a key mitotic spindle checkpoint regulator, MAD2, previously implicated in breast cancer. They found that when CHFR is absent, MAD2 does not do its job.

"Cells without CHFR not only have problems creating the structure or apparatus necessary to separate the chromosomes between the two daughter cells during cell division. They also have an impaired ability to detect and correct the problem before the chromosomes separate," says Privette.

"Prior to our findings, we knew that breast cancer cells often had the wrong number of chromosomes, but no one had identified any gene, or group of genes, that could account for the high frequency of this problem," says Privette.

The new study, she says, "provides one reason why the majority of breast cancer cells have too many chromosomes, which is a major hallmark of malignant cancers. Although a lot of work remains, and other genes are likely involved, our work on the role of CHFR in breast cancer development is an interesting and important piece of a very large puzzle."

Source: University of Michigan Health System