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Breast cancer cells regulate multiple genes in response to estrogen-like compounds

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Cancer researchers have discovered a previously unknown type of gene regulation and DNA behavior in breast cancer cells that may lead to better insight about environmental exposure to estrogen-like compounds.

A new study, published in the journal Genome Research by researchers at The Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James), provides the first evidence that cells can regulate many genes at once by looping their DNA, contributing to cancer when it goes awry. In this study, the gene regulation was discovered in breast cancer cells as a response to the hormone estrogen and resulted in the silencing of 14 genes at one time.

Tim H.-M. Huang, professor of molecular virology, immunology and medical genetics in the OSUCCC-James human cancer genetics program, and Pei-Yin Hsu, a visiting scholar and researcher in Huang's lab, discovered the DNA looping event in a breast cancer cell line gene cluster at chromosome region 16p11.2. They validated the finding using normal human breast epithelial cells and two animal models.

In addition, they used the normal-cell model to determine if long-term exposure to nine estrogen-like chemicals can initiate gene silencing through this mechanism. These chemicals included diethylstilbestrol, two thalates and bisphenol A (BPA).

The suppressive effects varied in normal cells. When the investigators

exposed a group of four rats to BPA for 21 days, however, they found concurrent suppression of ten genes comparable to those located at 16p11.2. These findings, says Huang, suggest that continuous exposure to estrogen-like compounds might lead to permanent silencing of genes located in this conserved cluster.

In healthy breast epithelial cells, 14 gene regulatory sites came together to form a single, temporary transcription site, Huang says. "But in breast cancer cells, there is no coordinated transcription site pairing, the DNA loops become tangled and the entire gene complex shuts down in a dead knot."

In some cases, Huang says, this multi-gene regulatory mechanism can increase gene expression and oncogenic activity, and further contribute to cancer development.

"We offer a new concept in this paper for the collective regulation of gene transcription," says first author Hsu, who identified the loop structures and their significance. "We found that in normal breast cells, DNA looping is more flexible and brings different promoters together temporarily. But in cancer, this complex just locks up and causes long-term suppression."

Researchers generally believe that transcription factors bind to a site on a single gene, and then the gene is actively transcribed, according to Huang. The study's findings show that this is not always the case. Sometimes the promoter is located far away, and it is remotely controlled.

"Overall, our study shows that certain regions of the genome are silenced because the DNA has lost flexibility, and that this inflexible DNA status might be a good marker for studying environmental exposure to estrogen-like compounds," Hsu says.

More information: The full paper, titled, "Estrogen-mediated epigenetic repression of large chromosomal regions through DNA looping" can be found in the June issue of the journal Genome Research.

Provided by Ohio State University Medical Center