Molecular trigger for breast cancer development identified

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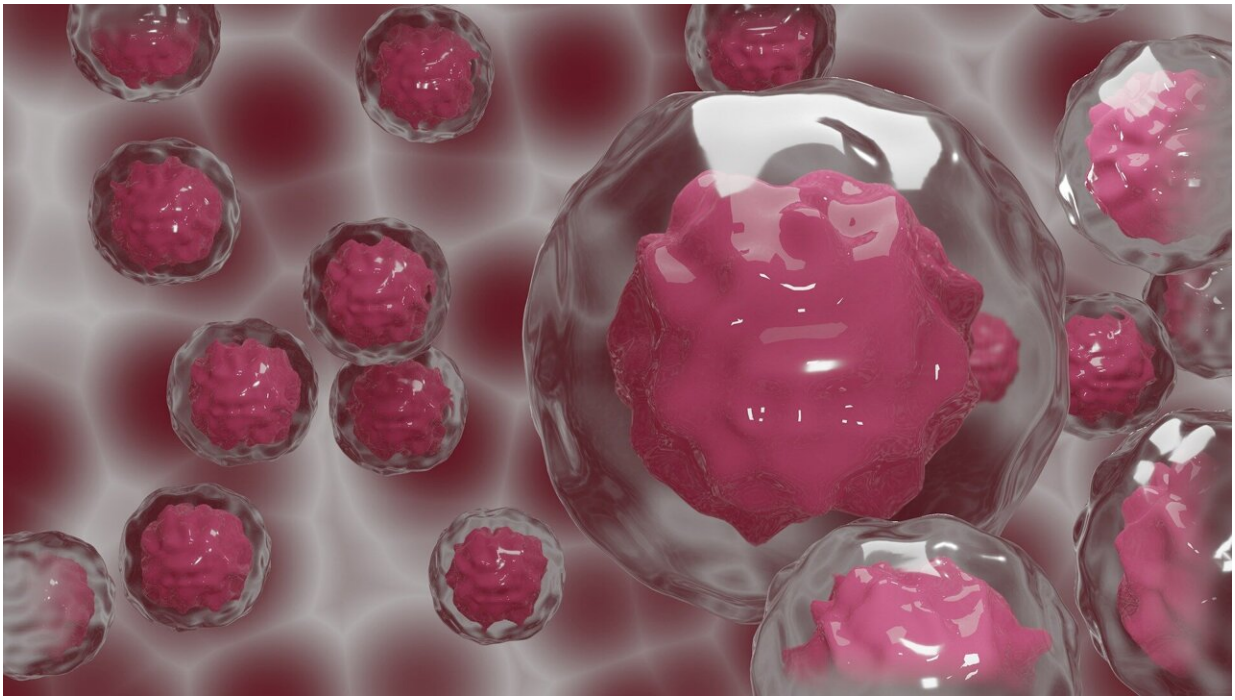

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In what may turn out to be a long-missing piece in the puzzle of breast cancer, Harvard Medical School researchers have identified the molecular sparkplug that ignites cases of the disease currently unexplained by the classical model of breast-cancer development. A report on the team's work is published May 17 in *Nature*.

"We have identified what we believe is the original molecular trigger that initiates a cascade culminating in breast tumor development in a subset of breast cancers that are driven by estrogen," said study senior investigator Peter Park, professor of Biomedical Informatics in the Blavatnik Institute at HMS.

The researchers said as many as one-third of breast cancer cases may arise through the newly identified mechanism.

The study also shows that the sex hormone estrogen is the culprit behind this molecular dysfunction because it directly alters a cell's DNA.

Most, though not all, breast cancers are fueled by hormonal fluctuations. The prevailing view of estrogen's role in breast cancer is that it acts as a catalyst for cancer growth because it stimulates the division and proliferation of breast tissue, a process that carries the risk for cancer-causing mutations. The new work, however, shows that estrogen causes mischief in a far more direct manner.

"Our work demonstrates that estrogen can directly induce genomic rearrangements that lead to cancer, so its role in breast cancer development is both that of a catalyst and a cause," said study first author Jake Lee, a former research fellow in the Park lab who is now a medical oncology fellow at Memorial Sloan Kettering Cancer Center.

Although the work has no immediate implications for therapy, it could inform the design of tests that can track treatment response and could help doctors detect the return of tumors in patients with a history of certain breast cancers.

Birth of a cancer cell

The human body is made up of hundreds of trillions of cells. Most of

these cells are constantly dividing and replicating, a process that sustains the function of organs day after day, over a lifetime.

With each division, a cell makes a copy of its chromosomes—bundles of tightly compressed DNA—into a new cell. But this process sometimes goes awry, and DNA can break. In most cases, these DNA breaks get swiftly mended by the molecular machinery that guards the integrity of the genome. However, every now and then, the repair of broken DNA gets botched, causing chromosomes to get misplaced or scrambled inside a cell.

Many human cancers arise in this manner during cell division, when chromosomes get rearranged and awaken dormant cancer genes that can trigger tumor growth.

One such chromosomal scramble can occur when a chromosome breaks, and a second copy of the broken chromosome is made before the break gets fixed.

Then, in what ends up being a botched repair attempt, the broken end of one chromosome is fused to the broken end of its sister copy rather than to its original partner. The resulting new structure is a misshapen, malfunctioning chromosome.

During the next cell division, the misshapen chromosome is stretched between the two emerging daughter cells and the chromosome "bridge" breaks, leaving behind shattered fragments that contain cancer genes to multiply and get activated.

Certain human cancers, including some breast cancers, arise when a cell's chromosomes get rearranged in this way. This malfunction was first described in the 1930s by Barbara McClintock, who went on to win the Nobel Prize in Physiology or Medicine in 1983.

Cancer experts can often identify this particular aberration in tumor samples by using genomic sequencing. Yet, a portion of breast cancer cases do not harbor this mutational pattern, raising the question: What is causing these tumors?

These were the "cold" cases that intrigued study authors Park and Lee. Looking for answers, they analyzed the genomes of 780 breast cancers obtained from patients diagnosed with the disease. They expected to find the classical chromosomal disarray in most of the tumor samples, but many of the tumor cells bore no trace of this classic molecular pattern.

Instead of the classic misshapen and improperly patched-up single chromosome, they saw that two chromosomes had fused, suspiciously near "hot spots" where cancer genes are located.

Just as in McClintock's model, these rearranged chromosomes had formed bridges, except in this case, the bridge contained two different chromosomes. This distinctive pattern was present in one-third (244) of the tumors in their analysis.

Lee and Park realized they had stumbled upon a new mechanism by which a "disfigured" chromosome is generated and then fractured to fuel the mysterious breast cancer cases.

A new role for estrogen in breast cancer?

When the researchers zoomed onto the hot spots of cancer-gene activation, they noticed that these areas were curiously close to estrogen-binding areas on the DNA.

Estrogen receptors are known to bind to certain regions of the genome when a cell is stimulated by estrogen. The researchers found that these estrogen-binding sites were frequently next to the zones where the early

DNA breaks took place.

This offered a strong clue that estrogen might be somehow involved in the genomic reshuffling that gave rise to cancer-gene activation.

Lee and Park followed up on that clue by conducting experiments with breast cancer cells in a dish. They exposed the cells to estrogen and then used CRISPR gene editing to make cuts to the cells' DNA.

As the cells mended their broken DNA, they initiated a repair chain that resulted in the same genomic rearrangement Lee and Park had discovered in their genomic analyses.

Estrogen is already known to fuel breast cancer growth by promoting the proliferation of breast cells. However, the new observations cast this hormone in a different light.

They show estrogen is a more central character in cancer genesis because it directly alters how cells repair their DNA.

The findings suggest that estrogen-suppressing drugs such as tamoxifen—often given to patients with breast cancer to prevent disease recurrence—work in a more direct manner than simply reducing breast cell proliferation.

"In light of our results, we propose that these drugs may also prevent estrogen from initiating cancer-causing genomic rearrangements in the cells, in addition to suppressing mammary cell proliferation," Lee said.

The study could lead to improved breast cancer testing. For instance, detecting the genomic fingerprint of the chromosome rearrangement could alert oncologists that a patient's disease is coming back, Lee said.

A similar approach to track disease relapse and treatment response is already widely used in cancers that harbor critical chromosomal translocations, including certain types of leukemias.

More broadly, the work underscores the value of DNA sequencing and careful data analysis in deepening the biology of cancer development, the researchers said.

"It all started with a single observation. We noticed that the complex pattern of mutations that we see in genome sequencing data cannot be explained by the textbook model," Park said. "But now that we've put the jigsaw puzzle together, the patterns all make sense in light of the new model. This is immensely gratifying."

More information: Peter Park, ERα-associated translocations underlie oncogene amplifications in breast cancer, *Nature* (2023). DOI: 10.1038/s41586-023-06057-w.
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