Notch2 Signaling: A Key Driver of Breast Cancer Dormancy in Bone Marrow

Research reveals how dormant breast cancer cells survive in bone marrow and evade therapy for years

CHINA, June 4, 2026 /EINPresswire.com/ -- Breast cancer can remain dormant in the bone marrow for decades before reactivating, resulting in cancer relapse. A study published in Bone Research unveils the critical role of Notch2 signaling pathway in promoting this dormant state. The study explains how dormant cancer cells mimic healthy stem cells and activate stress pathways to survive in the bone marrow—paving the way for innovative targeted therapies against dormant cancer cells.

Treating breast cancer remains a major medical challenge worldwide. This is largely due to the ability of breast cancer cells to remain hidden for years before triggering a relapse, which can occur even decades after successful treatment of the primary tumor. This occurs due to the transfer of a small amount of cancer cells to the bone marrow that enter a dormant or inactive state for long periods, after which they eventually "wake up" and aggressively cause secondary tumors in bone and other organs.

Scientists have long known that the bone marrow provides a protection site for these dormant cancer cells. But the mechanism behind the survival of these cells still remains unclear. Now, a research team led by Professor Anna Teti from the Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy, also affiliated with the National Council of Research, Italy, has uncovered new molecular pathways that regulate breast cancer cell dormancy in bones. The study was conducted in collaboration with Ludwig Maximilian University of Munich and the University of Southern Denmark, and the findings were made available online in Volume 14 of Bone Research on May 14, 2026.

Bone marrow contains specialized microenvironments known as "niches," which help regulate the behavior of stem cells. The endosteal niche is one such region, located near the bone surface which contains bone-forming cells called osteoblasts. Previous studies show that these niches may also shelter dormant cancer cells, but the mechanisms behind their shelter are poorly understood. In the present study, the researchers discovered that breast cancer cells appear to mimic certain properties of healthy stem cells in order to survive within these protective bone marrow environments.

"We discovered that breast cancer cells can exploit the same protective systems that normally

maintain healthy stem cells in bone marrow," explains Prof. Teti. "This allows cancer cells to remain hidden and potentially reactivate years later."

To investigate the underlying process, researchers studied two closely related signaling proteins, Notch1 and Notch2. Signaling proteins help cells communicate with their environment and control important cellular functions. The team discovered that even though both proteins are present in breast cancer cells, Notch2 plays the dominant role in dormancy. By combining imaging methods, gene expression analysis, and laboratory experiments, researchers found that breast cancer cells with high levels of Notch2 divided much more slowly while interacting with specialized osteoblasts in the endosteal niche. Slow cell division is a key feature of cellular dormancy. Whereas cells that have high levels of Notch1 did not show a similar dormant behavior.

The team then performed RNA sequencing, a technique used to analyze gene activity across the genome. They found that Notch2-rich cells showed lower activity of genes involved in cell growth and division, while activating genes associated with hematopoietic stem cells that produce blood cells in bone marrow. In particular, dormant cancer cells expressed high levels of CXCR4, CD34, and TIE2 (genes that help stem cells survive within the bone marrow niche). Further experiments showed that cells with high CXCR4 or TIE2 levels formed fewer and smaller bone tumors in mice, suggesting reduced cancer spread.

"This was a particularly interesting finding because it suggests that cancer cells can acquire stem cell-like properties to evade treatment and survive in the body for very long periods," remarks Prof. Teti.

Importantly, the cells with high Notch2 expression activated stress-response pathways known as the unfolded protein response, which helps cells survive under stressful conditions. These cells also showed elevated levels of molecules such as PERK, ATF4, CHOP, and CD177 (a newly identified marker linked to dormant breast cancer cells). Notably, CD177-high cells also showed high Notch2 and CXCR4 expression, showed reduced cell proliferation, and were associated with improved patient survival outcomes.

Altogether, this study provides new insights into how breast cancer cells survive silently in bone marrow for years before getting reactivated. The identification of Notch2, CXCR4, CD177, and stress-response pathways as key regulators of dormancy, leads to new possibilities for therapies aimed at eliminating dormant cancer cells or preventing their reactivation, thus significantly reducing the risk of cancer relapse in breast cancer patients.

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Reference
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About Professor Anna Teti from University of L'Aquila, Italy
Dr. Anna Teti has been a Professor of Histology at the Department of Biotechnological and Applied Clinical Sciences at University of L'Aquila, Italy. She earned her PhD in Biological Sciences in 1977 and her research focuses on bone biology, skeletal diseases, cancer metastasis to bone, and interactions between tumor cells and the bone microenvironment. Over her scientific career, she has published more than 240 research publications till date with over 11,000 citations. She is also a former President of the European Calcified Tissue Society and is internationally recognized for her contributions to bone and cancer research. She is now Senior Associate at the National Research Council Institute of Biochemistry and Cell Biology where she continues to investigate the mechanisms altering bone cell structure and function.

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