The Bone Microenvironment Role in Breast Cancer

BY DIBASH KUMAR DAS, PhD

Metastasis to distant organs is the key cause of cancer-related deaths. In estrogen receptor-positive (ER+) breast cancer, which accounts for 70 percent of all breast cancers, 20-40 percent of these patients will develop metastases (Cell 2021; https://doi.org/10.1016/j.cell.2021.03.011). In a majority of metastatic breast cancer cases, the bones are the first site of metastasis, much more frequently compared to the lungs, liver, and brain.

Genomic studies have suggested that bone may not be the final destination for cancer cell dissemination (J Clin Invest 2018; https://doi.org/10.1172/JCI96149). With some research showing that metastases will not be limited to the bone, but

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Task Force Finalizes New Colorectal Cancer Screening Recommendation

BY CHUCK HOLT

The U.S. Preventive Services Task Force has published a final recommendation statement calling for individuals to get their first colorectal cancer (CRC) screening at age 45 instead of waiting until age 50.

The new recommendation was announced in November and made in response to a nationwide increase in incidences of CRC among young adults. An independent panel of experts, the task force is appointed by the Department of Health and Human Services Agency for Healthcare Research and Quality, whose recommendations heavily influence decisions by policymakers.

The Centers for Medicare and Medicaid (CMS), which by law must pay for CRC screening for its recipients, and also insurance plans subject to rules under the Affordable Care Act, will follow the task force’s recommendation and cover the screenings.

The change is categorized as a B recommendation on the five-letter classification scale used by the task force. CRC screening for patients ages 55-76 remains strongly encouraged, making it an A recommendation. While screening for those

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Exploring the Link Between Inflammation & Leukemia

Two recent collaborative publications by CU Cancer Center members provide insights into how chronic inflammation can serve as a key factor in the development of leukemia and other blood cancers.

Eric Pietras, PhD, CU Cancer Center member and Assistant Professor in the CU School of Medicine Division of Hematology, and James DeGregori, PhD, Deputy Director of the CU Cancer Center and Professor in the Department of Biochemistry and Molecular Genetics, were corresponding authors on both papers.

Both papers provide support for the theory of adaptive oncogenesis, which was developed by DeGregori. The theory stipulates that chronic inflammation (such as the inflammation associated with aging or with chronic disease) reduces the fitness of normal cells, hindering their ability to reproduce and creating space for cells with cancer-causing mutations to proliferate.

Challenging Previous Understandings

The first paper, titled “PU.1 enforces quiescence and limits hematopoietic stem cell expansion during inflammatory stress,” was published in the Journal of Experimental Medicine (2021; doi: 10.1084/jem.20201169). Pietras’ laboratory technician, James Chavez, BS, as primary author, explored the effect of inflammation on the transcription factor PU.1 and its effect in turn on the production of hematopoietic stem cells (HSCs), the immature cells found in the bone marrow that can develop into blood cells.

Pietras noted this research challenged his previous understanding of

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rather subsequently occur in other organs and eventually cause death. Yet, how the bone microenvironment impacts ER signaling and endocrine therapy remains poorly understood.

One of the main objectives of the lab of Xiang Zhang, PhD, is to elucidate the biological mechanisms underlying why ER+ breast cancer metastasizes to the bone and spreads to other tissues despite effective endocrine therapies directed at the ER. Zhang serves as the William T. Butler, MD, Endowed Chair for Distinguished Faculty and Professor of Molecular and Cellular Biology in the Lester and Sue Smith Breast Center at Baylor College of Medicine.

Toward this end, Zhang and colleagues recently published two papers simultaneously where they applied a set of unique techniques and experimental models they previously developed to study interactions of cancer and bone at a single-cell resolution. This allows the team to understand how ER+ cancer cells escape endocrine therapies and what happens to these cells when they metastasize to the bone.

One of the studies was published in the journal Developmental Cell (2021; https://doi.org/10.1016/j.devcel.2021.03.008). Phenotypic plasticity is a critical factor in normal development, tumor initiation, and tumor progression. The heterogeneity of ER expression in ER+ tumors may signify such plasticity. Here, the team hypothesized those unique interactions between the bone microenvironment and ER+ disseminated tumors may allow for survival and therapeutic resistance.

The findings revealed that even genetically identical ER+ cancer cells display a considerable level of variation in ER expression. Using multiple approaches, including an evolving barcoding strategy, the team discovered that when ER+ breast cancer cells located in the bone, the osteogenic niche transiently and reversibly reduces ER expression activity, specifically in bone micrometastases, leading to increased stemness, and less susceptibility to endocrine therapies directed at ER.

The researchers determined that osteogenic cells promoted the phenotypic plasticity of metastatic ER+ both by releasing factors and by direct physical interaction with the cells. The authors noted that these properties increase the capability of cancer cells creating new metastasis.

Additionally, the team identified several metabolic pathways that were modified in cancer cells by the bone microenvironment. Among these pathways, the EZH2-mediated pathway drives ER+ breast cancer cells toward metastasis and a stem-like state. Many studies have underscored the role of EZH2 in cancer development and have demonstrated that EZH2 fosters cell survival, proliferation, invasion, epithelial to mesenchymal, and drug resistance of cancer cells. Consequently, EZH2-mediated epigenomic reprogramming is a leading candidate for therapeutic intervention.

A limitation of the study is that it did not address the question of whether the observed effects are specific to the bone microenvironment. Additionally, the study is also limited by the absence of naturally occurring murine ER+ models that recapitulate endocrine responses and development of resistance. These findings readily connected to a second study published in Cell (2021; https://doi.org/10.1016/j.cell.2021.03.011).

In this study the team investigated whether bone metastases, as compared to a primary tumor, were more likely to further disseminate to other organs. Using several methodologies, including parabiosis and an evolving barcode system, the researchers demonstrated that the bone microenvironment not only allows cancer cells to further spread, but also appears to augment this process. The researchers also showed that the bone microenvironment can galvanize other types of cancer, such as prostate cancer.

Moreover, they discovered that this metastasis-promoting effect is driven by an EZH2-mediated epigenomic reprogramming that maintains the dedifferentiated and stem-like status of breast cancer cells by repressing the lineage-specific transcriptional programs. The same findings also apply to single cell-derived populations, indicating mechanisms distinct from clonal selection.

Taken together, these studies revealed an unappreciated role of the bone microenvironment in metastasis progress, provided insights into the clinical enigma of ER+ metastatic recurrences despite endocrine therapies, and may lead to new treatments and strategies for resistant BCs.

“...the bone microenvironment may be a launching pad of cancer cells to further metastasize to multiple other organs. It will be important to study how to confine cancer cells in the bone and prevent further dissemination.”

—Xiang Zhang, PhD, Baylor College of Medicine

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