A novel strategy to potentially reduce breast cancer bone metastasis

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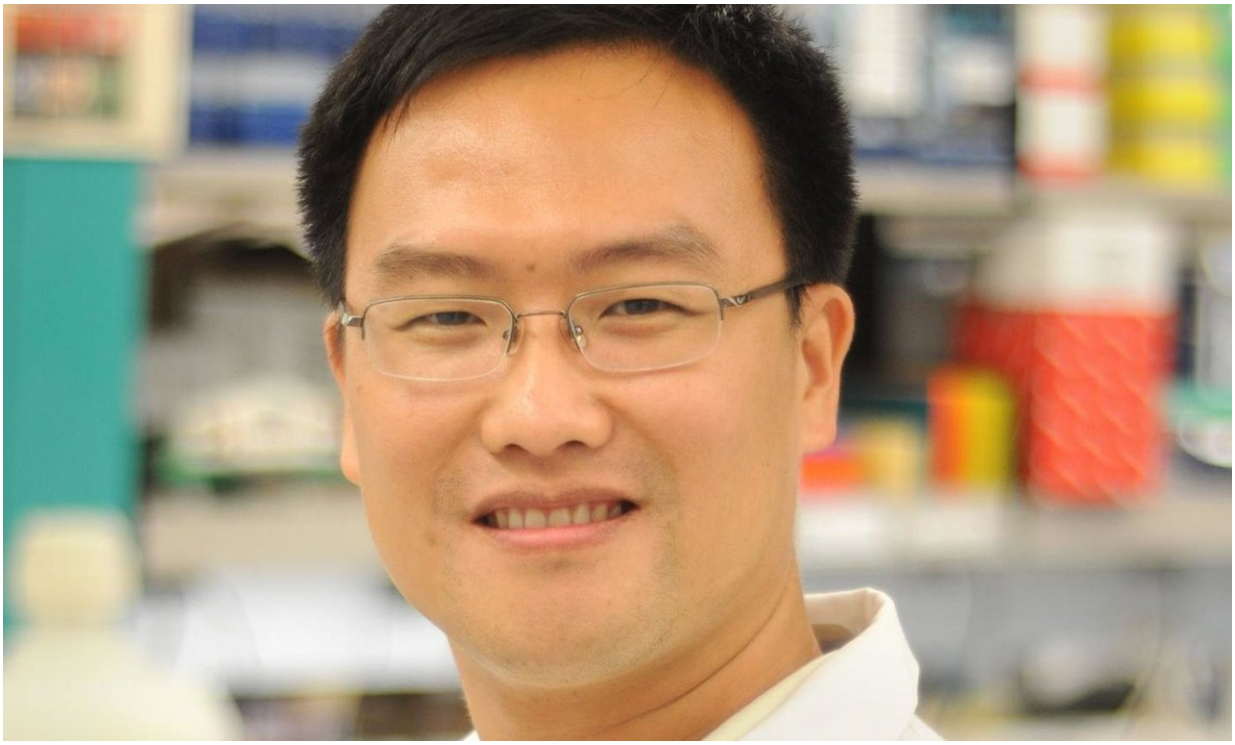

Dr. Xiang 'Shawn' Zhang. Credit: Baylor College of Medicine

Uncovering a novel mechanism that promotes growth of breast cancer bone metastasis has revealed a potential Achilles' heel for these cancer cells. Reported in the journal *Cancer Cell*, the study shows that interfering with this mechanism can reduce the risk of relapses in animal models.

"Metastasis is the dissemination of cancer cells from the original tumor location to other organs. In the case of breast cancer, bone is usually the most common site of metastasis," said first author Dr. Hai Wang, instructor at the Lester and Sue Smith Breast Center in the lab of Dr. Xiang 'Shawn' Zhang at Baylor College of Medicine.

Researchers have found that the bone microenvironment can promote the growth and progression of micrometastasis, a small group of cancer cells that separates from the original tumor and migrates to the bone. Bone support can contribute to full-blown metastasis that is strongly associated with poor prognosis.

"However, the early steps that encourage micrometastasis to grow and develop in this environment are not completely understood," said Zhang, who is associate professor of molecular and cellular biology and the Lester and Sue Smith Breast Center, and member of the Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine. "In this study, we further explored interactions between the bone microenvironment and cancer cells in bone metastasis."

Working with animal models and with cancer cells in the lab using their bone-in-culture array, an experimental system in which they can mimic the interactions between cancer cells and bone cells, the researchers determined that bone cells called osteogenic cells and cancer cells establish a physical connection through gap junctions. This connection works like a tunnel through which calcium travels from the osteogenic cell to the cancer cell. The transfer of calcium can promote the early outgrowth of tumor cells that could lead to major bone metastasis.

The 'seeds' and the 'soil'

"Blocking the calcium transfer that takes place through gap junctions as well as the activity of the mTOR pathway we previously determined

results in cancer cells dying or having difficulty growing because they are lacking the support of the osteogenic cells," said Zhang, who also is a McNair Scholar at Baylor and the corresponding author of this work. "This observation suggested a potential Achilles' heel in micrometastasis that could be targeted with medications to reduce the risk of full-blown metastasis."

In the lab, the researchers tested drugs that already have been approved for other conditions and found exciting results.

"A very short treatment that combined the drug everolimus, an mTOR inhibitor, and arsenic trioxide that affects calcium transport, significantly suppressed growth of bone metastasis in our mouse model," Zhang said.

"I think that conceptually, these results are telling us that when studying cancer biology, we cannot ignore the microenvironment. We do need to consider the 'seeds' and the 'soil' in its entirety, rather than studying the seeds separate from the soil," Wang said. "It was clear in our study that binding to bone cells rewires cancer cells so profoundly that they can become resistant to therapies they were expected to be sensitive to. They also may become sensitive to drugs that would not have been considered for cancer treatment."

"We hope that with this and other studies in the lab we can achieve a better understanding of the 'conversation' between cancer and bone marrow, so we can stop cancer cells before they become macrometastasis or disseminate to other places," Zhang said. "Although the drugs we tested have already been approved by the Food and Drug Administration to treat other conditions, there is still a number of steps that have to be fulfilled before they can be offered to treat micrometastasis in bone."

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