How the Stromal Microenvironment of Breast Tumors Affects Metastasis

BY WARREN FROELICH

A team led by Washington University researchers in St. Louis has identified a biological pathway within the stromal microenvironment of breast tumors that when inhibited not only reduces metastasis, but also limits some potentially devastating side effects of what’s been called the “vicious cycle” of chemotherapy—bone loss.

About 70 percent of patients with metastatic breast cancer experience the spread of their tumor to bones, by far the most common metastatic site for this cancer. Once in the bone, the disease is considered incurable, sometimes leading to painful and debilitating spinal cord compression, and significant increases in pathological fractures.

“Our findings indicate that we can limit metastatic tumor growth, extend survival, and at the same time limit cancer- and therapy-induced bone loss,” said Sheila A. Stewart, PhD, Professor of Cell Biology and Physiology and Associate Director for Basic Sciences with the Siteman Cancer Center at the Washington University School of Medicine. She presented her findings during a session on the “Evolving Tumor Microenvironment in Cancer Progression,” held online January 11-12, 2021, by the American Association for Cancer Research (AACR).

For the most part, chemotherapies used to treat cancer today target the tumor cells themselves. But in a series of preclinical and animal studies, Stewart and her collaborators instead turned their attention to the stromal compartment in breast cancer, and its spread to other parts of the body.

“It is important to understand that tumor cells ‘live’ in a community referred to as a tumor and that community contains many normal cells that have been corrupted to support tumor cell survival and/or migration out to other organs,” Stewart said.

“What we have learned is that tumor cells are often dependent on these ‘normal,’ if misguided cells,” she added. “Thus, we may be able to increase the impact of our anti-cancer strategies by targeting normal cells we collectively refer as stromal cells.”

Based on their pre-clinical results, Stewart and her team have been awarded a grant from the National Institute of Defense to lead a clinical trial to test a small molecule inhibitor of this pathway in breast cancer patients.

The inhibitor in question, called ATI-450, targets a protein called MK2 (mitogen-activated protein kinase-activated protein kinase 2), a protein kinase downstream from another protein called p38, a central regulator of inflammation that’s frequently found in tumor cells and surrounding stromal cells. Patients will receive oral doses of this small molecule inhibitor in combination with chemotherapeutic agents, either paclitaxel or capecitabine.

“As our therapies continue to improve patient outcomes, it will be incumbent on us to find ways to mitigate the negative impacts of our therapies,” Stewart said in an interview. “Our approach addresses one such negative impact—bone loss. If successful in the metastatic setting, then we might be able to move these drugs to the primary setting where patients also suffer bone loss after chemotherapy.”

Breast Cancer Findings

In her plenary talk, Stewart outlined results from several animal studies in her lab that have led to the upcoming proposed clinical trial. In essence, these experiments were based on the hypothesis that blocking the p38/MK2 pathway would limit tumor-promoting activities of the bone stromal compartment while simultaneously preserving bone quality, something current standard-of-care can’t achieve.

To test this idea, breast cancer tumor cells were introduced into laboratory mice, followed a day or two later by treatment with paclitaxel—one today’s standard-of-care chemotherapy—or a single agent inhibitor of p38.

These animal experiments showed that the p38 inhibitor was just as effective as paclitaxel in limiting tumor growth. Results with an inhibitor of MK2 yielded similar findings.

To determine where the p38 was acting, the researchers carried out two experiments in tumor cells. The first showed a reduction in cell growth with paclitaxel, as expected. However, when the cells were exposed to the p38 inhibitor, the tumor cells continued to grow just fine, demonstrating that p38 was not acting on the tumor cells themselves.

Then, with the aid of shRNA (short hairpin RNA) in tumor cells, the team demonstrated that p38 activity was taking place in the stromal compartment, suggesting its inhibition there would limit tumor growth. Stewart and colleagues performed similar experiments to determine if inhibition of MK2 would also reduce tumor growth.

“What you see are similar results to the p38 inhibitor,” she said. “We saw significant reduction in metastatic growth both within the bone as well as the visceral organs. So, we were pretty excited about this.

“We also saw that the animals were running around more than animals that were on paclitaxel. It really made us start thinking about the biology of what happens to, not just in our mice, but patients when they have metastatic lesions, particularly of the bone.”

Stewart concluded that p38 and MK2 inhibitors were both effective in preventing bone loss in animal models via suppression of p38/MK2-induced inflammatory cytokines and growth factors in the stromal compartment, breaking what’s been called the “vicious” cycle in bone metastasis.

Briefly, cancer cells that have spread to the bone release cytokines and growth factors that interfere with the normal bone-shaping process. These proteins stimulate the cells that break down bone (osteoclasts) and make them overactive. So, bone is destroyed faster than it’s rebuilt.

“People think of this as the vicious cycle in which the tumor cells are actually creating more food for themselves so they can increase growth,” Stewart said.

Indeed, the researchers noticed that animals treated with paclitaxel alone experienced a reduction in tumor growth, but at a significant cost in bone density. However, the bones of animals treated with the p38 or the MK2 inhibitors were, for the most part, preserved.

“So, the p38 and MK2 inhibitors are basically two-for-one,” she said during her talk. “On the one hand, both are able to limit the stromal support for tumor growth and on the other hand they are able to protect the bones.”

Further, because stromal cells do not undergo the same changes in DNA as tumor cells, it is also possible that they will be less likely to escape treatment as tumor cells do.

“Thus, our strategies may also be more durable (i.e. last longer),” Stewart said.

Future studies are aimed at identifying which cell types within the bone contribute to tumor growth and bone loss.

“We find numerous differences that could explain how the stromal compartment contributes to tumor progression and bone loss and how inhibition of p38 and MK2 contribute,” Stewart said in her abstract. “These data underscore the vital role stromal-derived factors play in tumor progression and identify the p38-MK2 pathway as a promising therapeutic target for metastatic disease and prevention of tumor-induced bone loss.”

Warren Froelich is a contributing writer.