Study suggests new strategies against bone metastases from prostate cancer

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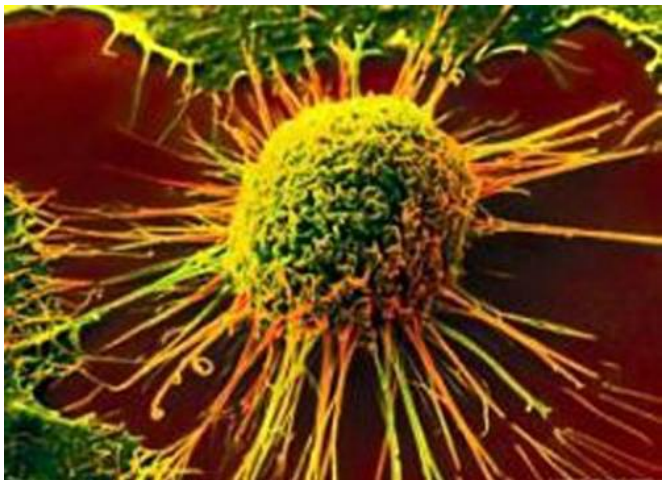

When prostate cancer spreads, it most often spreads to bone. And while the 5-year survival rate for prostate cancer that has not spread is nearly 100 percent, once the disease reaches bone, the 5-year survival rate is only 29 percent. Now a University of Colorado Cancer Center study published in the *Journal for Immunotherapy of Cancer* suggests a new approach, or, possibly two new approaches against these bone metastases: While targeted therapies and anti-cancer immunotherapies have not been especially successful against primary prostate cancers, the study suggests that both these approaches may be effective against the bone metastases that grow from primary prostate cancers, and, in fact, the type of bone metastasis may dictate which targeted therapies and immunotherapies work best.

There are two types of bone disease from metastases: lytic metastases, which destroy bone tissue, and blastic metastases, which build new bone-like tissue with cancer cells. Currently, it doesn't matter if a bone metastasis is lytic or blastic—they are both treated the same way. But the current study shows that the genetic and cellular landscapes of these two types of metastases are different, providing different drug targets and suggesting different treatments.

"The genetic and immune checkpoint changes are like those seen in other solid tumors, making it potentially possible to apply new strategies to prostate cancer patients with metastatic bone disease," says paper first author Claire Ihle, Ph.D. student in the lab of CU Cancer Center investigator and paper senior author Philip Owens, Ph.D.

Lytic metastases were characterized by over-activity in a genetic signal called pAKT and its larger signaling pathway called PI3K-AKT, both of which have been targets for drug development in other cancers. Meanwhile, blastic lesions had over-activity in another genetic signal called pSTAT3 and its signaling pathway JAK-STAT, for which FDA-approved drugs already exist.

"I was really shocked by the increase in pSTAT3 in the blastic patients. I expected that these bone-producing (blastic) lesions would have little to no specific targets. I am glad I was wrong as these are the most common lesions in prostate cancer patients," Ihle says. "I would love to see STAT3 inhibitors go to blastic-type patients if we have more data showing a good response."

Importantly, both types of bone metastases also had characteristics that predict response to immunotherapy. Doctors and researchers call primary prostate cancers "cold," meaning they tend not to provoke an immune response. However, both blastic and lytic bone metastases had high levels of the protein PD-L1, which could mean they are more likely to respond to the class of anti-cancer immunotherapy known as checkpoint inhibitors.

"The other interesting point of our studies is that we developed a test that can directly measure immunotherapy and pathway targets in bone metastases," Owens says. "This is significant because we could potentially use this as a test to determine which of the many immunotherapies could be best for an individual patient, one at time, and truly provide a personalized therapy. If I had metastatic disease in bones, I would like a pathology department to know that the immunotherapy they wish to treat me with has a good level of target in the tissue they are hoping to treat."

The group is now focused on testing therapies in mouse models of lytic and blastic bone metastases to determine the most promising drugs and drug combinations.

"The pathway-targeted therapies could be used in combination with immunotherapy or alone and we really don't know if or how to combine them," Owens says.

Previously, the field assumed that bone metastases could be treated the same as the primary prostate cancers from which they grow. Now, the current study shows that's not the case, and even pinpoints signaling pathways and immunologic weaknesses of various types of metastases. If these findings stand the test of ongoing work, the line of research may point to new therapies and drug combinations for these metastases that represent the most dangerous aspects of prostate cancer.

More information: Claire L. Ihle et al, Distinct tumor microenvironments of lytic and blastic bone metastases in prostate cancer patients, *Journal for ImmunoTherapy of Cancer* (2019). DOI: 10.1186/s40425-019-0753-3

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