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New model can predict therapy outcomes in prostate cancer with bone metastasis

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A new computational model that simulates bone metastasis of prostate cancer has the potential to rapidly assess experimental therapy outcomes and help develop personalized medicine for patients with this disease, according to data published in *Cancer Research*, a journal of the American Association for Cancer Research.

"Bone remodeling is a balanced and extremely well regulated process that controls the health of our bones and the levels of circulating calcium," said Leah M. Cook, Ph.D., postdoctoral fellow in the Department of Tumor Biology at the Moffitt Cancer Center in Tampa, Fla. "Active prostate cancer cells in the bone environment can speak the same language of the bone remodeling cells, and disrupt the delicate bone remodeling process. They promote extensive bone destruction and formation that in turn yields nutrients, allowing the prostate cancer cells to grow, thus creating a vicious cycle."

"The mathematical model we created simulates this vicious cycle, and allows us to predict the impact of potential therapies on cancer cells and normal cells of the bone," said Arturo Araujo, Ph.D., postdoctoral fellow in the Department of Integrated Mathematical Oncology at the Moffitt Cancer Center. "Unlike biological models, we can freeze the mathematical model at any time point in order to explore what each cell is doing at that particular point in time."

To create the computational model, which they call "hybrid cellular automata," Araujo, Cook, and colleagues created simulations of

different cell types involved in bone metastasis of prostate cancer, including two types of bone cells called osteoclasts and osteoblasts, and prostate cancer cells. They then created algorithms to simulate the interactions of these cells among themselves and with other bone metastasis-related factors in the microenvironment, including the proteins TGF-beta, RANKL, and other bone-derived factors.

The researchers found that when they introduced a single metastatic prostate cancer cell to the model, it was able to simulate bone metastasis seven out of 25 times, accurately creating the vicious cycle. This phenomenon is difficult to reproduce using preclinical animal models, which is critical in determining the best time to apply therapies in order to obtain maximum efficiency, explained Araujo.

Further, the fact that the model failed to generate a bone lesion 18 out of 25 times reflects reality, where not every metastatic cancer cell that invades bone in prostate cancer patients succeeds in forming a viable lesion, he added.

In parallel to developing the computational model, the researchers grew prostate cancer cells that metastasize to bone in mice and found that the tumor growth rate predicted by the computational model was comparable to the tumor growth rate in mice, thus validating their simulations. The model was also able to identify some critical players and events in the process of bone metastasis.

To test if the model could predict treatment outcomes, they applied two standard-of-care treatments, bisphosphonates and an anti-RANKL therapy, and found that the anti-RANKL therapy fared better than bisphosphonates, which is what is seen in prostate cancer patients with bone metastasis treated with these therapies, according to Araujo. The model predicted that improving the efficacy of anti-RANKL delivery to the prostate cancer-bone microenvironment might yield better outcomes.

With further improvements, the model can be individualized to determine personalized medicine for prostate cancer patients, Araujo noted.

"By integrating mathematics with robust biological data, we are beginning to develop powerful tools that allow us to rapidly assess how factors contribute to prostate cancer progression in bone," said Araujo. "Ultimately, we feel that the ability to customize these models based on inputs from each patient's cancer biopsy will help medical oncologists determine the best treatment strategies, so that significant improvements in survival and quality of life can be made."

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