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Study reveals genetic chain reaction that drives the spread of prostate cancer

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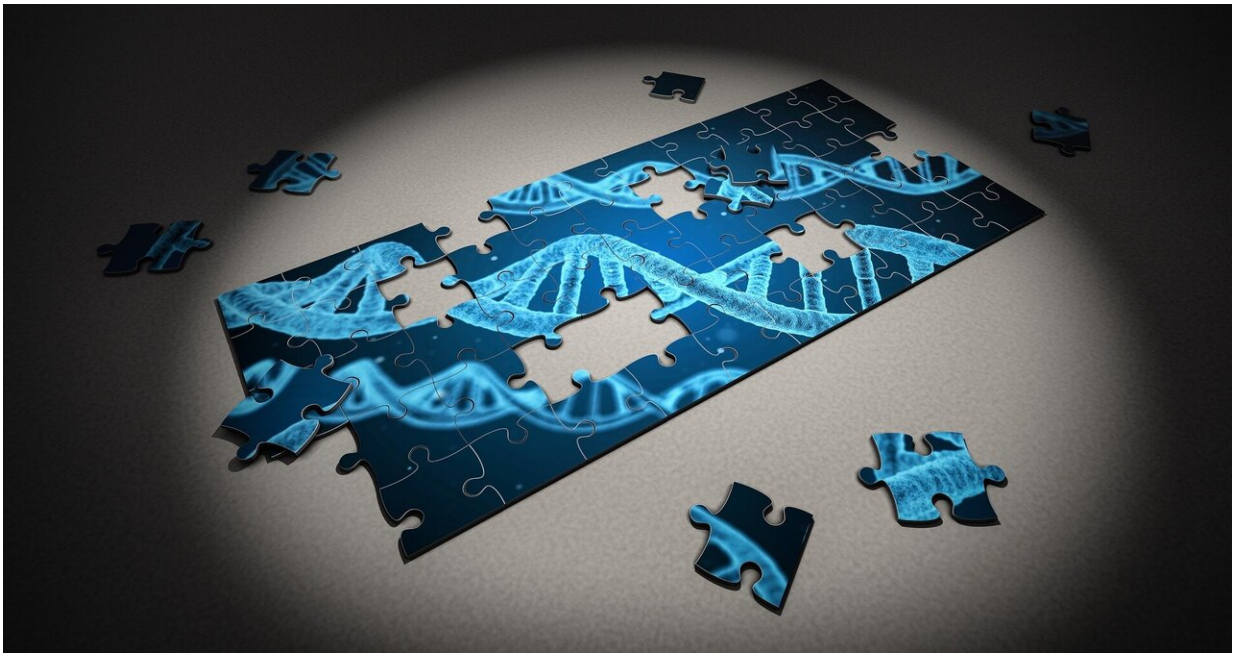

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New research from scientists at VCU Massey Comprehensive Cancer Center and the VCU Institute of Molecular Medicine (VIMM) determined that a particular gene—MDA-9/Syntenin-1/SDCBP—is the ringleader behind a molecular domino effect driving prostate cancer growth and metastasis. The findings could hold significant clinical implications for the treatment of prostate cancer and other forms of

disease.

The study—published Nov. 3 in the *Proceedings of the National Academy of Sciences*—aimed to understand the role of the MDA-9 gene in prostate cancer and how this gene communicates with surrounding cells and tissue in the tumor microenvironment to cause the tumor to migrate into the bones.

Bone metastasis is common in all types of advanced cancer, but particularly among patients with prostate and breast tumors. Once the cancer is in the bones, it drastically deteriorates bone health, often leading to fractures, breaks and other life-threatening complications.

"The final stages of cancer resulting in metastases are invariably fatal; there are virtually no curative options once a patient's cancer has metastasized to the bone," said one of the study senior authors Paul B. Fisher, M.Ph., Ph.D., FNAI, the Thelma Newmeyer Corman Endowed Chair in Cancer Research at Massey and director of the VIMM.

Extensive research previously conducted by Fisher and his collaborators identified that the MDA-9 gene—a gene that is not specific to tumor cells and is found in all forms of tissue—is a major contributor to the spread of cancer; however, the biological "why" remained unknown.

Through this new study, the scientists for the first time ever demonstrated that MDA-9 is largely responsible for initiating a cellular chain reaction that sparks prostate cancer metastasis and empowers the tumor cells to take over control in the bone itself.

"MDA-9 plays a role from A to Z in the tumor; it is essentially the gene that directly facilitates tumor progression and metastasis," said Swadesh K. Das, Ph.D., another senior author on this paper, member of the VIMM, Massey scientist and an associate professor in the Department of

Human and Molecular Genetics at the VCU School of Medicine.

Through this study, they identified that MDA-9 activates a protein known as PDGF-AA in tumor cells, which regulates cell growth and division, and releases it into the bone environment. Then, PDGF-AA binds with receptors (PDGFR) on the surface of a type of bone marrow cells known as bone marrow-mesenchymal stromal cells (BM-MSCs).

These interact with MDA-9 to activate the Hippo signaling pathway, which is responsible for cell regeneration. This releases a smaller migration-stimulating protein known as a chemokine, in this case CXCL5. CXCL5 then attracts cancer cells into the bone tissue, which in turn interact to produce more CXCL5 and continue to draw more cancer cells into the environment, causing a cyclical chain of events that bolsters the growth of disease in bone.

Additionally, as CXCL5 is luring more tumor cells into the tissue, it is also causing the deterioration and fracture of the bones by enhancing the reproduction of osteoclasts, a subset of bone cells that destroy the bone.

"This study is a definitive demonstration of communication between prostate cancer cells and normal BM-MSCs within the tumor microenvironment, and how this biological conversation between them allows for metastatic cells to spread to and proliferate in bone," Das said.

By eliminating MDA-9 in prostate cancer cells, the researchers interrupted this genetic game of telephone that leads to tumor growth and prevented the spread of disease. The researchers also observed that removing MDA-9 from bone cells did not negatively affect the health of bone tissue.

In this study, the interaction was observed in animal, human and patient-derived prostate cancer cells, but the researchers believe these findings

will hold implications for a variety of solid tumor types in which MDA-9 is also present, including brain, breast, melanoma, lung and pancreatic cancers, among others.

"We're close to something that may go into the clinic," Fisher said, adding that they have developed a novel inhibitor drug in-house at VCU in collaboration with InVaMet Therapeutics that has previously shown promise through separate studies in targeting MDA-9 in cancer.

Future research is planned to investigate the use of MDA-9 inhibitors in clinical tumor samples and, ultimately, in patients.

More information: Santanu Maji et al, MDA-9/Syntenin in the tumor and microenvironment defines prostate cancer bone metastasis, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2307094120

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