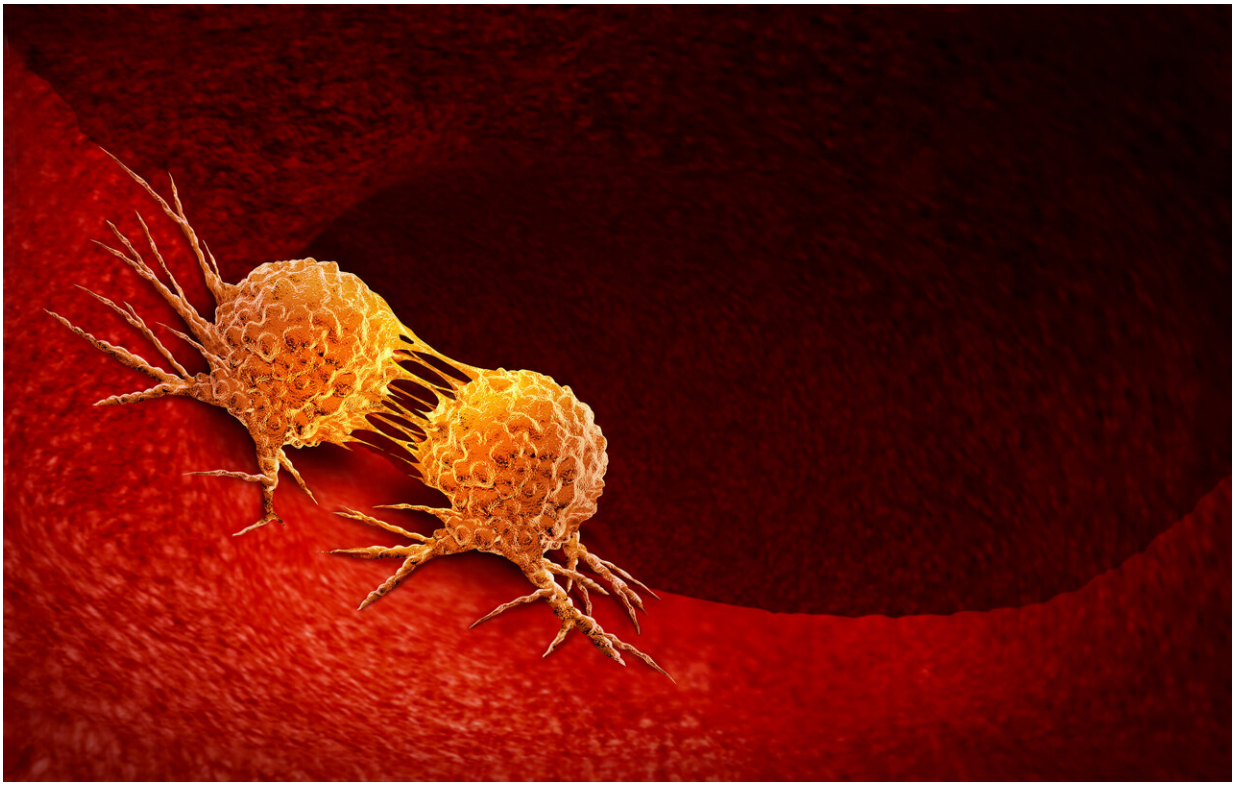
MedicalXpress

PAD4 inhibition in neutrophils halts cancer progression and metastasis

September 7 2022



Cancer Cell Dividing. Credit: The Wistar Institute

Researchers in the laboratory of Yulia Nefedova, M.D., Ph.D., at The Wistar Institute and collaborators at Jubilant Therapeutics Inc. have uncovered a novel mechanism by which protein arginine deiminase 4 (PAD4) in neutrophils promotes cancer progression. The paper also

found that inhibition of this function of PAD4 reduces primary tumor growth and metastasis and enhances checkpoint inhibitor treatments. Jubilant Therapeutics Inc. is developing a novel small molecule PAD4 inhibitor that directly targets this mechanism. The findings appear in *Cancer Research*.

"Development of metastases remains a leading cause of death from cancer. Tumor-associated neutrophils have long been implicated in cancer progression. Understanding the mechanisms by which these cells promote tumor growth and metastatic spread is critically important for the development of new treatments," shares Yulia Nefedova, M.D., Ph.D., associate professor, Immunology, Microenvironment & Metastasis Program, Ellen and Ronald Caplan Cancer Center of The Wistar Institute.

This research revealed the importance of PAD4 protein in the migration of neutrophils, specialized white blood cells that serve as the first line of immune defense in the body, directly impacting both primary tumor growth and secondary malignant tumor spread. Both genetic deletion of PAD4 and pharmacological inhibition of PAD4 using Jubilant Therapeutic Inc's novel inhibitor dramatically down-regulated chemokine CXCR2, reduced immune suppressive polymorphonuclear myeloid derived suppressor cells (PMN-MDSCs) at tumor and metastatic sites, activated T cells, and synergized with immune checkpoint blockade.

All results point to a potent anti-tumor effect of PAD4 inhibition to target PMN-MDSCs in the tumor microenvironment. This finding is being further investigated in Wistar's Nefedova laboratory.

"These results highlight the potential of PAD4 inhibition as a novel treatment approach for cancer in addition to the previously established role of this pathway in autoimmune diseases," said Luca Rastelli, Ph.D.,

Chief Scientific Officer, Jubilant Therapeutics Inc. "We are developing several highly selective oral, small molecule PAD4 inhibitors, with the goal of bringing this novel mechanism to the clinic as potential therapeutics for tumor metastasis in colorectal and pancreatic cancers, patients with liver metastasis as well as for both acute and chronic autoimmune/inflammatory diseases."

More information: Yulia Nefedova et al, Regulation of tumor progression by PAD4-mediated neutrophil migration and its targeting with a novel selective inhibitor JBI-589, *Cancer Research* (2022). DOI: 10.1000/CAN-21-4045R1

Provided by The Wistar Institute