Low-dose, four-drug combo blocks cancer spread in mice

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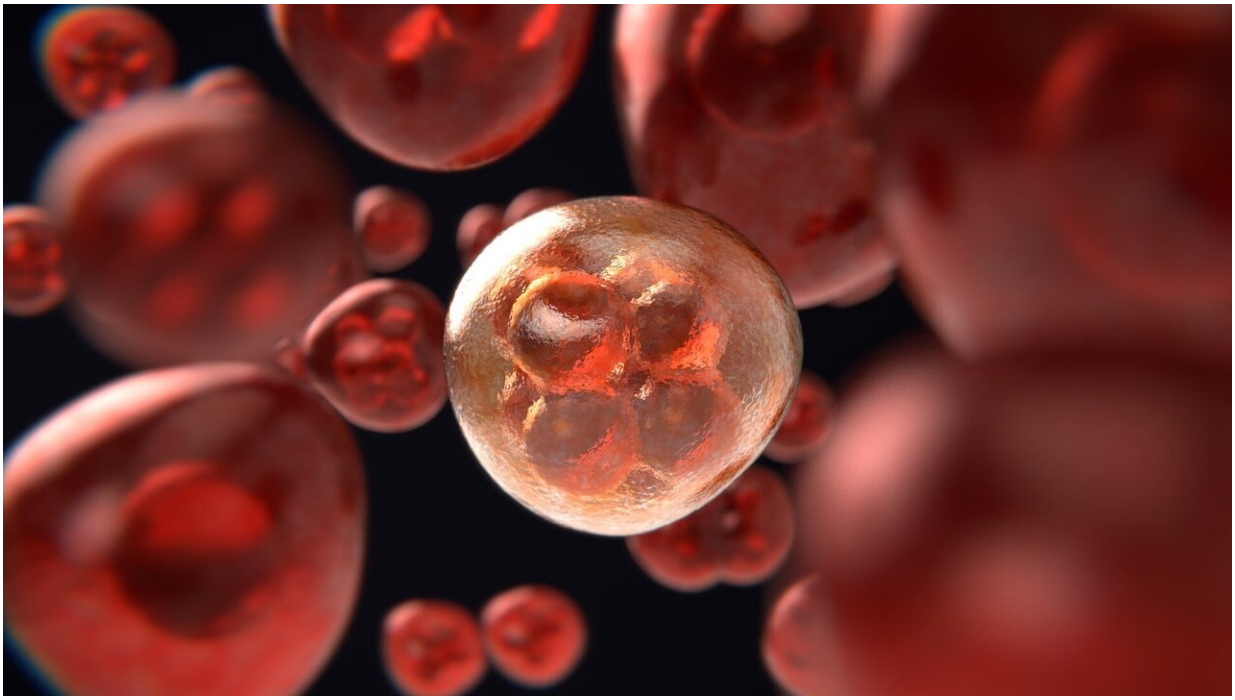

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Low doses of a four-drug combination helps prevent the spread of cancer in mice without triggering drug resistance or recurrence, shows a study published today in *eLife*.

The findings suggest a new approach to preventing cancer metastasis in patients by simultaneously targeting multiple pathways within a

metastasis-promoting network. They may also help identify people who would most likely benefit from such treatment.

Metastasis, the spread of cancerous cells through the body, is a common cause of cancer-related deaths. Current approaches to treating metastatic cancer have focused on high doses of individual drugs or drug combinations to hinder pathways that promote the spread of cancer cells. But these approaches can be toxic to the patient, and may inadvertently activate other pathways that cause the drugs to stop working and the tumors to return.

"There is an urgent need for new strategies to suppress cancer metastasis, especially for cancers such as triple-negative breast cancer that currently lack effective therapies," says first author Ali Yesilkanal, a postdoctoral scholar at the Ben May Department for Cancer Research at the University of Chicago, US.

In the study, Yesilkanal and colleagues analyzed gene expression data from patients participating in the Cancer Genome Atlas study to understand how a metastasis-suppressing protein called Raf Kinase Inhibitory Protein (RKIP) works. They found that RKIP reduces the expression of a network of genes that promote the spread of cancer cells.

They then created a four-drug combination that mimics how RKIP suppresses the ability of cancer cells to spread. They administered low doses of this treatment to mice with metastatic cancer that mimics metastatic breast cancer, and found that it blocked the spread of cancer and increased the animals' survival. Importantly, the treatment did not trigger the compensatory mechanisms that often cause high-dose, anti-metastasis drugs to stop working and tumors to return.

Finally, the team used computer modeling to explain why reducing, but not completely stopping, the expression of this network of genes helped

prevent metastasis without triggering drug resistance or relapse. They also identified patients with breast cancer in the Cancer Genome Atlas who might be most likely to benefit from such treatment based on their cancer's gene expression patterns.

"Our findings could lead to a new cancer treatment strategy where patients first receive low-dose combination drugs that block metastasis and then receive traditional cancer treatments such as radiation, chemotherapy or immunotherapy," says co-senior author Marsha Rosner, the Charles B. Huggins Professor at the Ben May Department of Cancer Research at UChicago.

"Our results challenge current approaches to cancer treatment and suggest an alternative strategy for controlling metastasis in breast cancer and potentially other types of cancer," concludes co-senior author Alexandre Ramos, Group Leader at the School of Arts, Sciences and Humanities, University of São Paulo, Brazil.

More information: Ali Ekrem Yesilkanal et al, Limited inhibition of multiple nodes in a driver network blocks metastasis, *eLife* (2021). DOI: 10.7554/eLife.59696

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