To stop cancer's spread, take out its communication channels

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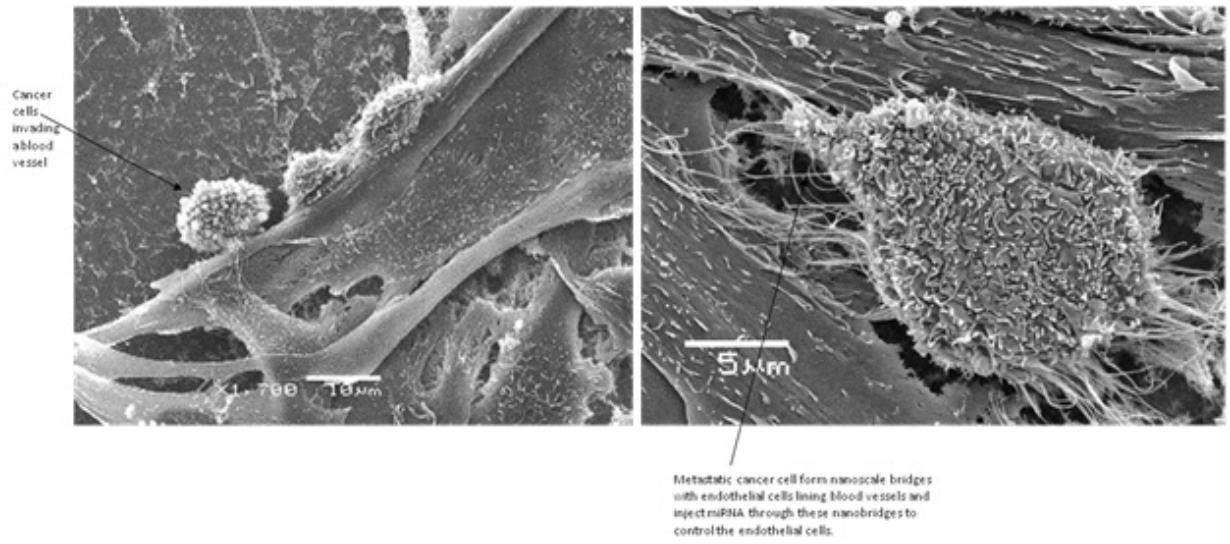

Metastatic cancer cells form nanoscale bridges with endothelial cells lining blood vessels and inject miRNA through these nanobridges to control endothelial cells. Credit: Shiladitya Sengupta, Brigham and Women's Hospital

Metastasis - or the spread of cancer from one part of the body to other parts - accounts for more than 90 percent of cancer-related deaths. Although the cells that seed metastasis and the sites that they tend to travel to have been increasingly studied over the years, little has been known about how cancer migrates from a primary site, such as breast tissue, to a secondary site, such as the brain or bone marrow. A study by researchers from Brigham and Women's Hospital (BWH), published in

Nature Communications, offers a new view of how cancer cells extend their reach, co-opting and transforming normal cells through "metastatic hijacking." The researchers also find that in pre-clinical models, pharmacological intervention can prevent this hijacking from occurring, pointing to new therapeutic targets for preventing cancer cells from spreading.

"Metastasis remains a final frontier in the search for a cure for cancer," said Shiladitya Sengupta, MS, PhD, of BWH's Bioengineering Division in the Department of Medicine and corresponding author of the study. "For the past five years we have studied how cancer travels to other parts of the body, and what we find is that communication is key."

"By working together, our labs have been able to gain greater insights into cell-cell communication in tumor states, which will shed new light on cancer as a disease and the promise and potential of emerging innovative therapies," said Elazer Edelman, MD, PhD, of BWH's Cardiovascular Division in the Department of Medicine.

Sengupta, Edelman and colleagues began with a simple experiment. In the lab, they constructed a three-dimensional tumor matrix, complete with endothelial cells, and added metastatic breast cancer cells. They observed that instead of adhering to themselves to form a sphere, the metastatic breast cancer cells spread out along the model's blood vessels. Using a scanning electron microscope, the researchers detected long, thin tubes extending outward from the cells - nanoscale bridges that connected the cancer cells to normal tissue. The researchers found that the molecular profiles of some of the normal, endothelial cells had been changed, and hypothesized that microRNAs were being transferred over the bridges into the endothelial cells. Upon closer examination, they found that the transformed endothelial cells now harbored two microRNAs that have previously been implicated in metastasis.

The researchers then used chemical compounds to prevent the nanoscale bridges from forming, disrupting communication between the tumor cells and endothelium. They did so in the laboratory constructed model and also in a mouse model, finding that pharmacological agents, including docetaxel, which is used to treat metastatic breast cancer, decreased the number of nanoscale bridges formed by the cells. In mice pre-treated with the pharmacological agents, the researchers observed a significant decrease in metastatic tumor burden.

In future studies, the researchers will look to see if ATPase inhibitors - drugs that have been studied for treating HIV-AIDS - may also be effective at preventing the bridges from forming and inhibiting metastasis.

"Our study opens up new avenues for exploration and suggests that these nanoscale membrane bridges may represent new therapeutics in managing metastatic breast cancer," said Sengupta. "We plan to continue searching for and evaluating treatments that take aim at these conduits."

More information: Connor Y et al. "Physical nanoscale conduit-mediated communication between tumor cells and endothelium modulates endothelial phenotype." *Nature Communications* DOI: 10.1038/NCOMMS9671

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