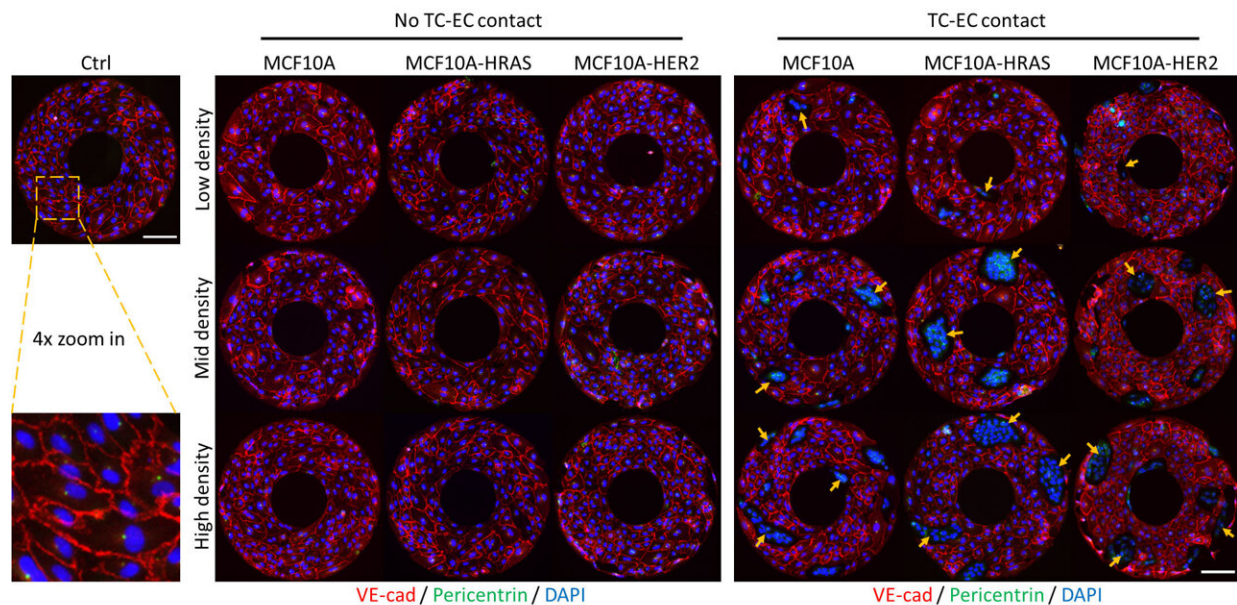


How metastatic cancer causes leaky blood vessels

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Immunofluorescence images showing the effects of contactless paracrine signaling interactions (left) or physical contact (right) in micropatterned endothelial cells and tumor cells. Credit: Jie Fan

Preventing metastasis—the development of cancer cells beyond their original location—remains one of the major goals of current cancer research. Most malignant tumor cells metastasize by exploiting abnormal leakage from blood vessels. New work looks to further explore the role of how the alignment of endothelial cells, which line blood vessels, plays

a role in the spread of cancer.

In *APL Bioengineering*, researchers from the University of Michigan-Dearborn, Rensselaer Polytechnic Institute, and the University at Albany–SUNY developed a model that examines the local communication between [endothelial cells](#) and tumors cells and its effects on endothelial cell orientation. The approach involves the use of co-cultured human umbilical vein endothelial cells (HUVECs) and breast epithelial tumor cell lines to simulate the tumor-endothelial interaction.

"The [blood vessels](#) in tumor tissues are much leakier than those in normal tissues," said author Jie Fan. "We are curious whether the [tumor cells](#) can induce the weakening in the clockwise orientation of endothelial cells and cause them to disorganize in the vessel."

The work expands on recent findings that showed that endothelial cells have chirality, a type of mirrored-image orientation similar to right and left hands, and they tend to skew in a clockwise direction.

"We believe the strong clockwise chirality of endothelial cells is important to maintain blood vessel integrity, but unfortunately, it could be damaged/weakened by tumor cells, which may increase the risk of metastasis," Fan said. "Preserving the normal chirality could inhibit tumor transmigration by reinforcing the chirality and the integrity of the endothelial barrier of blood vessels."

To address the question, the group co-cultured HUVECs with a series of tumor cell lines with varying degrees of malignancy. They then compared how HUVECs responded when the tumor cells were directly touching them versus not. To exert such a degree of control, they employed a contact printing technique to create either donut- or figure-eight-shaped micropatterns to hold the cells.

The group found the clockwise chirality of the HUVECs was less affected by local hormone signaling and more so by direct physical contact with tumor cells. Specific proteins on the tumor cell binding to others on endothelial cells appeared to play a role in changing the clockwise chirality of HUVECs.

The group was surprised by the movement of the cell types. In most models for metastasis, it is thought that tumor cells march toward blood vessels before breaking through into the bloodstream.

"We had expected the tumor cell would invade the endothelial cell," Fan said. "However, we found the endothelial cells were moving towards the tumor cell on the micropattern."

Fan said regulating this interaction holds promise for better controlling cancer metastasis and he hopes to work further on developing therapeutics toward this end.

The article "Interacting with [tumor](#) cells weakens the intrinsic clockwise [chirality](#) of endothelial cells" is authored by Benson Hang, Eman Jassem, Hanan Mohammed, Leo Q. Wan, Jason I. Herschkowitz, and Jie Fan. The article appears in *APL Bioengineering* on Dec. 6, 2022.

More information: Benson Hang et al, Interacting with tumor cells weakens the intrinsic clockwise chirality of endothelial cells, *APL Bioengineering* (2022). [DOI: 10.1063/5.0115827](https://doi.org/10.1063/5.0115827)

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