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# Study suggests tumors may 'seed' cancer metastases earlier than expected

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A new study from scientists at The Scripps Research Institute (TSRI) helps explain why cancer metastasis is so hard to stop.

The researchers found an additional mechanism explaining how a molecule long linked to cancer progression appears to "seed" the body with metastatic cells long before doctors would typically detect a primary tumor. The molecule, known as epidermal growth factor receptor (EGFR), encourages blood vessel growth early in tumor development—not only feeding the primary tumor, but also providing vehicles for cancer to escape the primary tumor site and travel throughout the body.

"When cancer cells have high levels of EGFR, the tumor has a lot of new, angiogenic blood vessels," said TSRI Assistant Professor Elena Deryugina, senior author of the new study. "And these vessels are very welcoming for tumor cells and facilitate their dissemination from the very early stages of tumor development."

The study was published recently in the journal *Neoplasia*.

## EGFR is Behind New Blood Vessel Growth

A previous study, led by Deryugina and TSRI Professor James Quigley, had shown that, compared with tumors expressing low levels of EGFR, high-level-EGFR tumors delivered 10- to 100-times more tumor cells to

secondary organs.

"When we downregulated EGFR so it wasn't expressed anymore, the tumor cells were not able to disseminate efficiently," said TSRI Research Associate Petra Minder, who was first author of the new study. "This gave us a hint that EGFR plays a role in intravasation [an early step of metastatic dissemination during which tumor cells enter angiogenic blood vessels]—we were just not sure how."

The new study shows how EGFR levels make a difference. In experiments using chick embryos, the researchers found that EGFR signaling started a chain reaction inside tumor cells, ultimately resulting in the release of a molecule called vascular endothelial growth factor (VEGF), known to be active in almost all forms of solid tumors. Released VEGF then binds to endothelial cells, inducing the growth of new blood capillaries and vessels within a developing tumor.

## What This Means for Cancer Treatment

For many years, scientists had seen small blood vessels growing in early-stage tumors, but it was thought these vessels were mostly for supplying tumors with oxygen and nutrients.

"Now we have learned that these newly formed vessels are used by tumor cells for dissemination because of their certain structural properties," added Deryugina.

The new study shows that these vessels are actually useful for tumors because they are dilated and unusually permeable. Tumor cells can slip into the vessels, escape the primary tumor site and lodge throughout the body. Escaped cells often lie dormant or grow very slowly, not appearing as metastases until after the primary tumor is detected.

The results could also explain why EGFR-inhibiting drugs have had limited success in human patients. While these drugs target EGFR's effects in primary tumor growth, they don't address EGFR's role in blood vessel growth and early metastatic seeding.

The researchers said the findings highlight the urgent need for new methods to diagnose cancers early and new treatments to fight growing metastases.

**More information:** Petra Minder et al. EGFR Regulates the Development and Microarchitecture of Intratumoral Angiogenic Vasculature Capable of Sustaining Cancer Cell Intravasation, *Neoplasia* (2015). DOI: 10.1016/j.neo.2015.08.002

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