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Research supports an alternate theory of how tumors metastasize

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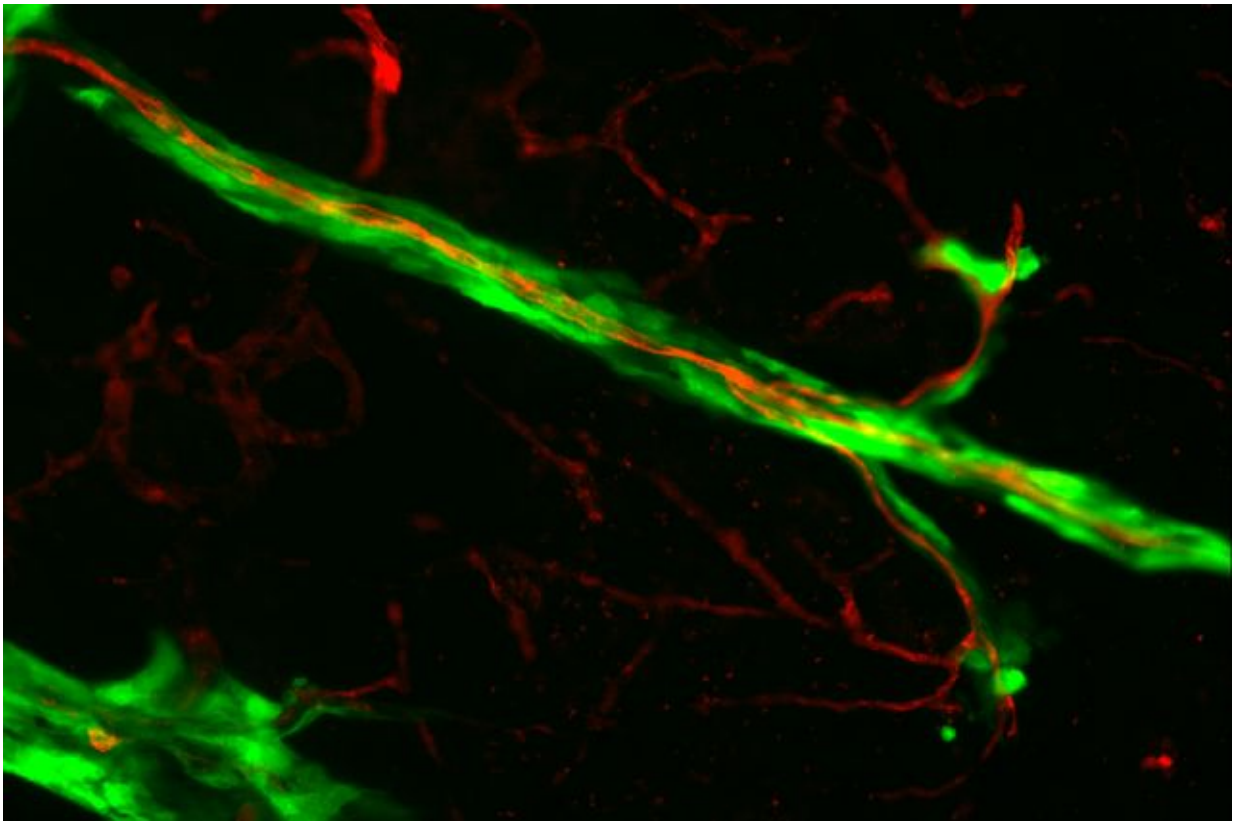

The scientists used a technique called confocal fluorescence microscopy to produce 3-D images of melanoma cells (green) spreading along the external surfaces of blood vessels (red). Credit: Laurent Bentolila, Roshini Prakash, Raymond Barnhill and Claire Lugassy

Scientists at the California NanoSystems Institute at UCLA have taken a

major step toward confirming an unusual theory of how some cancer cells metastasize. Their findings may lead to new strategies for keeping melanoma from spreading.

A commonly held theory about how cancer spreads is that tumor cells break off from the primary tumor and travel through the bloodstream to reach other organs, where they attach and grow into new tumors. But questions about that process have remained because circulating tumor cells in the blood sometimes have a short lifespan, and because of a lack of knowledge about how the cells leave the bloodstream and attach to organs.

The research team was led by Laurent Bentolila, director of UCLA's Advanced Light Microscopy/Spectroscopy lab, and included Claire Lugassy and Raymond Barnhill (formerly of UCLA and now of France's Institut Curie). They theorized that—in addition to the prevailing theory about how cancer spreads—tumor cells also could spread through the body by a mechanism called angiotropism, meaning that they could travel along the outside of blood vessels, without entering into the bloodstream.

Over the past decade, Lugassy and Barnhill gathered proof that tumor cells, especially those of the deadly skin cancer melanoma, creep along the outside of blood vessels like tiny spiders to spread cancer. They also found that the migrating cancer cells mimicked pericytes—cells that line the capillary blood vessels—which prevented the cancer cells from being killed by the human immune system.

The research by Bentolila's team marks the first time that these migrating cells have been imaged in 3-D.

To do the imaging, the scientists infused blood vessels with red fluorescent dye while human melanoma cells, which were dyed green,

were injected into the brain of a mouse. They used a microscopic technique called confocal fluorescence microscopy, which provides true three-dimensional optical resolution, to create 3-D images in which the dyed tumor cells and the vessels glowed under specific light. The images showed the cells begin to grow as a primary tumor at the injection site. Soon, the researchers observed the green cells spreading from the tumor and migrating along the outer surfaces of the red-dyed blood vessels.

"Lugassy and Barnhill's research on angiotropism has questioned the assumption that all metastatic tumor cells break off and flow through the bloodstream to spread disease," Bentolila said. "If tumor cells can spread by continuous migration along the surfaces of blood vessels and other anatomical structures such as nerves, they now have an escape route outside the bloodstream."

If tumor cells are found circulating in the bloodstream, Bentolila said, doctors might prescribe chemotherapy.

"But if the metastasizing cells are on the outside of the blood vessels," he said, "they escape exposure to the treatment and continue to spread cancer."

The findings will enable researchers to seek new targets for deadly cancers such as glioma, glioblastoma, pancreatic cancer, prostate cancer and gynecological carcinosarcomas.

More information: Laurent A. Bentolila et al. Imaging of Angiotropism/Vascular Co-Option in a Murine Model of Brain Melanoma: Implications for Melanoma Progression along Extravascular Pathways, *Scientific Reports* (2016). DOI: 10.1038/srep23834