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Stemlike cells at tumor perimeter promote new blood vessels to feed tumor growth

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Cancerous tumors need nutrients to grow, so they secrete factors promoting new blood-vessel formation to feed themselves. Researchers have long known that cells in low-oxygen environments at the center of the tumor send out these factors, but a new study by University of Illinois researchers found that stemlike cells at the edge of melanoma tumors secrete them, too – particularly when the cells are under strain from a tumor's complex topology.

Published in the journal *Science Advances*, the finding illustrates cancer's robustness in response to stresses, and points to new considerations for assessing tumors and developing treatments that target blood-vessel formation, a process called angiogenesis.

"The flexibility of cancer is one of the big dangers," said Kristopher Kilian, a professor of bioengineering and of materials science and engineering who led the research. "Cancer can adapt itself to establish optimal roots, to coordinate its own viability and dissemination. In our laboratory conditions, we see a broad spectrum of various factors secreted, but with further study we could identify which ones are more prevalent, look at different cancers and subtypes of cancers, and try to profile secreted molecules that you'd want to inhibit as cancer therapy."

Kilian's group previously demonstrated that when the periphery of a melanoma tumor is highly curved and cells are compacted, the cancer cells at the edges behave like stem cells. The researchers called them melanoma-initiating cells for their ability to spread and seed new tumors.

In the new study, the researchers looked at these stemlike cells again to see which combination of signaling chemicals they produced.

The team used melanoma microtumors grown in engineered environments that simulate conditions within body tissues. The tumors took a variety of shapes. The researchers compared periphery cells strained into curved shapes and cells from smoother tumors to see if the strain affected what the cells secreted.

"Cells exposed to strained topologies at the perimeter secreted much higher levels of growth factors that promote blood vessels," Kilian said. "And they did this at normal oxygen levels using the same pathway that we see in low-oxygen cells at the center of tumors, but in this case mechanical cues are responsible."

The researchers then looked at melanoma tumors in mice, again comparing those with curved edges and those that were more even. Kilian's group collaborated with Wawrzyniec Lawrence Dobrucki, a professor of bioengineering and head of the Molecular Imaging laboratory at the Beckman Institute for Advanced Science and Technology. They used a tracer that can monitor angiogenesis in live animals and saw that there was a significant increase in angiogenesis around melanoma-initiating cells at the edges of tumors with strained topology.

This is the first time a link has been established between stem cell-like melanoma-initiating cells and angiogenesis, Kilian said.

"This is important for prognosis and for therapeutic development," Kilian said. "If you're aiming at one target when there's multiple targets, you may be missing a culprit. Low oxygen is still important, but so is looking at the physical properties of the miroenvironment when you're looking at a tumor to assess what might be the most dangerous spots, as

well as designing therapies that might disrupt its growth."

Kilian's group is working to verify its results in human tissue and collaborating with physicians at the Mayo Clinic in Rochester, Minnesota, to explore differences among melanoma tumors from different patients.

"Seeing if we can observe and classify these melanoma-initiating cells and secretion profiles in human melanoma is the best next step forward to identifying a way to disrupt it. We are also interested in seeing if these things hold true for other cancers," Kilian said.

More information: Junmin Lee et al. Melanoma topology reveals a stem-like phenotype that promotes angiogenesis, *Science Advances* (2017). DOI: 10.1126/sciadv.1701350

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