Shape of tumor may affect whether cells can metastasize

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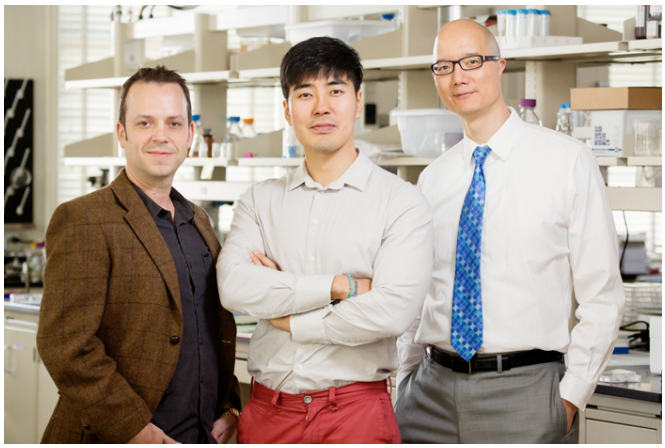

Illinois researchers found that the shape of a tumor may play a role in how cancer cells become primed to spread. From left: materials science and engineering professor Kristopher Kilian, graduate student Junmin Lee and veterinary medicine professor Timothy Fan. Credit: L. Brian Stauffer

Only a few cells in a cancerous tumor are able to break away and spread to other parts of the body, but the curve along the edge of the tumor may play a large role in activating these tumor-seeding cells, according to a new University of Illinois study.

Using engineered tissue environments in various shapes and patterns, the study of skin cancer found that the more curved the cell cultures were, the more cancer cells at the edges displayed markers of stem cell characteristics - the key to spreading to other tissues. This has potential for furthering our understanding of cancer as well as developing personalized treatment plans.

Led by Kristopher Kilian, a professor of materials science and engineering, and Timothy Fan, a professor of veterinary medicine, the researchers published their findings in the journal *Nature Materials*.

"The most dangerous part of cancer is metastasis," Kilian said. "Some cells that we call cancer stem cells adopt deadly characteristics where they can travel through the bloodstream to other tissue and form new tumors. There's a need for ways to find these cells and to study them, and importantly, to develop drugs that target them, because these cancer stem cells are resistant to chemotherapy drugs that target the main tumor. This causes recurrence: The cancer comes back."

Kilian's group specializes in tissue engineering to create models of tumors, in order to more accurately study cancer processes in a culture dish. In the new study, the researchers cultured mouse skin-cancer colonies on various 2-D and 3-D environments of different shapes and patterns to see if the tumor shape contributes to activation of cancer stem cells, and to see where in the tumor the stem cells appeared.

They found that cancer stem cells seemed to appear in the highest numbers along the edges of the engineered tumor environments, particularly where there were corners and convex curves.

"It was actually quite surprising," Kilian said. "Normal stem cells prefer a soft, squishy, internal position. So for cancer, everyone had assumed that the cancer stem cells were in the middle of the tumor. We found that geometric constraints, like you would have where a tumor touches healthy tissue, seem to activate these cancer stem cells at the perimeter."

The researchers did a number of tests in their engineered environments to confirm tumor-spreading ability, such as genetic analysis. They also tested other cancer lines - human cervical, lung and prostate cancers - and found that they responded to the patterned tumor environments in the same way.

Then Kilian's group teamed with Fan's group to test

the skin-cancer stem cells in live mice, and found that the cells taken from the patterned environments were much more likely to cause tumors than cells taken from a conventional flat dish.

"We found that many more mice developed tumors when given the cells that we had engineered to have these stem cell characteristics, and they had a much higher incidence of metastasis in the lungs," Kilian said. "In a tumor, similarly, regions that develop these kinds of shapes may activate cells that can then escape and form more tumors. This may allow surgeons to look at the perimeter of a growing tumor and use the shape to guide their assessment of which regions could be more problematic - where they need to take out more tissue around the tumor and where they may not need to take as much."

Kilian hopes that the patterned, engineered tissue environments will give researchers a new way to find and culture cancer stem cells, which have been very elusive in conventional cultures - less than 1 percent of cells, he said. Beyond the fundamental science of finding and understanding these cancer-spreading cells, he also sees engineered tumor environments as having therapeutic applications in personalized medicine.

"You can imagine a patient has a particular tumor. You could engineer that in a dish, and using the patient's own cells, you could develop a model of their specific tumor to test out drugs," he said. "If you could take a patient's cells and within days have microtumors that you could use to screen all the available drugs, then an oncologist would be able to prescribe a treatment that's tailor-made for the patient that targets both the tumor cells and these elusive cancer stem cells that currently we can't see.

"There's a lot more work to be done, but we're very excited about how a very simple materials property of a growing tumor might be a culprit of the disease spreading. We think it opens up a new avenue of investigation for drug development, guiding surgery, and understanding progression and spreading of cancer," Kilian said. "Cancer is very complex, so putting it in context is key. If there is a microenvironment that provides the context for activating cells that can spread cancer, then that's important to know."

More information: Junmin Lee et al, Interfacial geometry dictates cancer cell tumorigenicity, *Nature Materials* (2016). DOI: 10.1038/nmat4610

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