New way to grow, isolate cancer cells may add weapon against disease

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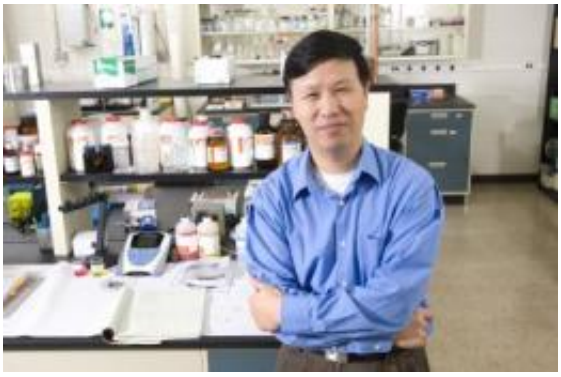

Ning Wang, a University of Illinois mechanical engineering professor, co-led a study showing that tumor-spreading cancer cells grow better in a soft substrate, much like stem cells. Credit: Jason Lindsey

A new method to isolate and grow the most dangerous cancer cells could enable new research into how cancer spreads and, ultimately, how to fight it. University of Illinois researchers and collaborators in China found that while a traditional culture of cancer cells has only a few capable of starting new tumors, a soft gel is capable of isolating tumor-repopulating cells and promoting the growth and multiplication of these cells in culture. The new culture technique could allow researchers to better study metastatic cancers.

The news a cancer patient most fears is that the disease has spread and become much more difficult to treat. A new method to isolate and grow

the most dangerous cancer cells could enable new research into how cancer spreads and, ultimately, how to fight it.

University of Illinois researchers, in collaboration with scientists at the Huazhong University of Science and Technology in China, published their results in the journal Nature Materials.

"This may open the door for understanding and blocking metastatic colonization, the most devastating step in cancer progression," said Ning Wang, a professor of mechanical science and engineering who co-led the study.

The most dangerous cancer cells are the ones that can break away from the primary tumor and travel through the body to form a new tumor in another tissue, a process called metastasis. Fortunately, only a small percentage of cancer cells have the ability to become new tumors. Unfortunately, the tumor-seeding cells are the ones hardest to kill with chemotherapy – and it only takes a lone survivor to mount a resurgence.

Cancer researchers have theorized that these elusive tumor-spreading cells may be responsible for recurrences after surgery or treatment. They are very interested in studying these cells in hopes of better understanding and ultimately combating them. However, identifying and isolating metastatic cells from a general cancer cell population is very difficult.

One hotly debated question is whether metastatic cells share characteristics of stem cells, and if so, to what extent. Some studies have found cancer cells with stem-cell markers, others have displayed stem-cell-like behavior, and yet others have suggested that cells can spontaneously switch from a primary cancer cell to a stem-cell-like cancer cell and back.

Wang's group at the U. of I. had previously found that stem cells grow better in a soft gel than on a rigid plate. They wondered if this principle would also apply to cancer-spreading cells, since they share some other qualities of stem cells. So they suspended single cells of mouse melanoma, a type of skin cancer, in soft gel made of fibrin, a fiber-like protein found throughout the body. They cultured the cells into colonies and compared them with those grown on a stiff flat surface, the traditional method used by cancer researchers.

After five days, the soft gels were riddled with spheres of soft cells, many more colonies than grew on the harder surface. In addition, the cells were softer and grew in spherical clumps – unusual for most cancer cells, but signature characteristics of stem cells.

"Starting from single cells, by day five, you have more cells in the soft substrate proliferating," Wang said. "This is exactly the opposite from most cancer cells, which prefer a stiffer substrate. But these cells like to grow in the soft environment. Why is this important? Because they turn into tumors."

The researchers found that the cells grown in the 3-D soft fibrin were much more efficient at causing tumors in mice than cells prepared traditionally. In fact, injecting as few as 10 cells from a culture grown in a soft gel was sufficient to induce tumors in a large percentage of mice, while 10,000 cells from a traditional culture are needed to achieve results with the same incidence of cancer. This suggests that, while a traditional culture of cells has only a few capable of starting new tumors, the soft substrate method is capable of isolating these cells and promoting the growth and multiplication of these cells in culture.

The researchers then tested their soft fibrin substrate with other cancer cell lines and found that they also formed stem-cell-like colonies of highly tumorigenic cells, showing that the process is generalizable for

many types of cancer. The cells grown in a soft gel even caused tumors in normal mice, called "wild-type," rather than only the immune-compromised mice typically needed for such studies.

The researchers also found that the tumor-repopulating cells express a self-renewal gene called Sox2, which is usually only expressed in stem cells and not in traditionally prepared cancer cells. When the researchers blocked the Sox2 gene, the cells started to differentiate, becoming traditional tissue-specific cancer cells.

Now, the researchers will continue exploring the molecular mechanisms that make these tumor-seeding cells so good at surviving in distant organs and so efficient at seeding tumors. They hope that knowledge will contribute to treatments to stop the spread of cancer.

"Since these cells are more resistant to current cancer-killing drugs than differentiated cancer cells, we would like to see if there are ways to identify and develop new molecules and methods that can specifically target and kill these cells," Wang said.

More information: The paper, "Soft Fibrin Gels Promote Selection and Growth of Tumorigenic Cells," is available online at www.nature.com/nmat/journal/va … t/full/nmat3361.html

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