Nanotech researchers discover cancer cells 'feel' much softer than normal cells

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A multidisciplinary team of UCLA scientists were able to differentiate metastatic cancer cells from normal cells in patient samples using leading-edge nanotechnology that measures the softness of the cells.

The study, published Dec. 2, 2007 in the advance online edition of the journal *Nature Nanotechnology*, represents one of the first times researchers have been able to take living cells from cancer patients and apply nanotechnology to analyze them and determine which were cancerous and which were not. The nano science measurements may provide a potential new method for detecting cancer, especially in cells from body cavity fluids where diagnosis using current methods is typically very challenging. The method also may aid in personalizing treatments for patients.

When cancer is becoming metastatic, or invading other organs, the diseased cells must travel throughout the body. Because the cells need to enter the bloodstream and maneuver through tight anatomical spaces, cancer cells are much more flexible, or softer, than normal cells. These spreading, invading cancer cells can cause a build-up of fluids in body cavities such as the chest and abdomen. But fluid build-up in patients does not always mean cancer cells are present. If the fluid could be quickly and accurately tested for the presence of cancer, oncologists could make better decisions about how aggressive a treatment should be administered or if any treatment is necessary at all.

In this study, researchers collected fluid from the chest cavities of

patients with lung, breast and pancreatic cancers, a relatively non-invasive procedure. One problem with diagnosing metastatic disease in this setting is that cancer cells and normal cells in body cavity fluids look very similar under an optical microscope, said Jianyu Rao, a researcher at UCLA's Jonsson Cancer Center, an associate professor of pathology and laboratory medicine and one of the study's senior authors. Conventional diagnostic methods detect about 70 percent of cases where cancer cells are present in the fluid, missing about 30 percent of cases.

"We detect cancer cells typically by looking at them under a microscope after the cells are fixed and stained with chemicals, which is really an antiquated method," Rao said. "Usually the cancer cells have larger nuclei and other subtle features. However, the normal cells from body cavity fluids can look almost identical to cancer cells under an optical microscope. While staining for tumor protein markers could increase diagnostic accuracy, what we were missing was a way to determine if cancer cells have different mechanical properties than normal cells."

Employing one of the most valuable tools in the nanotechnology arsenal, the research team used an Atomic Force Microscope (AFM) to measure cell softness. Since the cells being analyzed were less than half the diameter of a human hair, researchers needed a very precise and delicate instrument to measure resistance in the cell membrane, said James Gimzewski, professor of chemistry and biochemistry, a member of the California NanoSystems Institute and also one of the study's senior authors.

"We had to measure the softness of the cell without bursting it," Gimzewski said. "Otherwise, it's like trying to measure the softness of a tomato using a hammer."

The AFM uses a minute, sharp tip on a spring to push against the cell surface and determine the degree of softness. Think of it as an extension

of a doctor's hands performing a physical examination to determine disease, Gimzewski said.

"You look at two tomatoes in the supermarket and both are red. One is rotten, but it looks normal," Gimzewski said. "If you pick up the tomatoes and feel them, it's easy to figure out which one is rotten. We're doing the same thing. We're poking and quantitatively measuring the softness of the cells."

After probing a cell, the AFM assigns a value that represents how soft a cell is based on the resistance encountered. What the team found was that the cancer cells were much softer than the normal cells and they were similarly soft with very little variation in gradation. The normal, healthy cells from the same specimen were much stiffer than the cancer cells and, in fact, the softness values assigned to each group did not overlap at all, making diagnosis using this nanomechanical measurement easier and more accurate.

"It was fascinating to find such striking characteristics between the metastatic cancer cells and normal cells," said Sarah Cross, a graduate student in the chemistry and biochemistry department and a study author. "The metastatic cancer cells were extremely soft and easily distinguishable from the normal cells despite similarities in appearance. And we're looking at live cells taken from human patients, so that makes this is a unique finding."

Calvin Quate of Stanford University, the co-inventor of the Atomic Force Microscope, said the UCLA study breaks new ground.

"This manuscript is the first that directly shows a relationship between the nanomechanical properties and physiological function in clinical samples from patients with suspected cancer," said Quate, 1992 Medal of Science recipient.

National breast cancer expert Susan Love said the study findings “open a new era for function-based tumor cell diagnostics.”

“With these findings, it is foreseeable that a combined biochemical, biophysical and morphological analysis for analyzing human cytological specimens using AFM may be finally realized,” said Love, president and medical director of the Susan Love Research Foundation and a clinical professor of surgery at UCLA.

Researchers next will explore whether the nanomechanical analysis can be used to personalize cancer treatment based on the characteristics of a patient’s cancer cells. There are standard chemotherapy drugs that are used to treat metastatic cancer, Rao said, but response varies from patient to patient. If researchers could test the cancer cells beforehand, they could potentially apply therapies that would make the cells stiffer, making it more difficult for the diseased cells to spread through the body.

Source: University of California - Los Angeles