Harnessing Nanoparticles To Track Cancer Cell Changes

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The more dots there are, the more accurate a picture you get when you connect them. Cancer researchers adopting that philosophy have developed a new imaging technology that could give scientists the ability to simultaneously measure as many as 100 or more distinct features in or on a single cell. In a disease such as cancer, that capability would provide a much better picture of what is going on in individual tumor cells.

A Stanford University School of Medicine team led by Cathy Shachaf, Ph.D., has for the first time used specially designed dye-containing nanoparticles to simultaneously image two features within single cells. Although current single-cell flow cytometry technologies can provide up to 17 simultaneous visualizations, this new method has the potential to do far more. The new technology works by enhancing the detection of ultraspecific but very weak patterns, known as Raman signals, that molecules emit in response to light.

In a study published in the online journal *PLoS ONE*, the Stanford team was able to simultaneously monitor changes in two intracellular proteins that play crucial roles in the development of cancer. Successful development of the new technique may improve scientists' ability not only to diagnose cancers—for example, by determining how aggressive a tumor's constituent cells are—but also eventually to separate living, biopsied cancer cells from one another based on characteristics indicating their stage of progression or their degree of resistance to chemotherapeutic drugs. That would expedite the testing of treatments targeting a tumor's most recalcitrant cells, said Dr. Shachaf, a cancer researcher who works in a laboratory run by the study's senior author Garry P. Nolan, Ph.D., a member of the Center for Cancer Nanotechnology Excellence Focused on Therapy Response.

Cancer starts out in a single cell, and its development is often heralded by changes in the activation levels of certain proteins. In the world of cell biology, one common way for proteins to become activated is through a process called phosphorylation, which slightly changes a protein's shape, in effect, turning it on. Two intracellular proteins, Stat1 and Stat6, play crucial roles in the development of cancer. The Stanford team was able to simultaneously monitor changes in the phosphorylation levels of both proteins in lab-cultured myeloid leukemia cells. The changes in Stat1 and Stat6 closely tracked those demonstrated with existing visualization methods, establishing proof of principle for the new approach.

Although the new technology so far has been used only to view cells on slides, it could eventually be used in a manner similar to flow cytometry, the current state-of-the-art technology, which lets scientists visualize single cells in motion. In flow cytometry, cells are bombarded with laser light as they pass through a scanning chamber. The cells then can be analyzed and, based on their characteristics, can be sorted and routed to different destinations within the cytometer.

Still, flow cytometry has its limits. It involves tethering fluorescent dye molecules to antibodies, with different colors tied to antibodies that target different molecules. The dye molecules respond to laser light by fluorescing—echoing light at exactly the same wavelength, or color, with which they were stimulated. The strength of the fluorescence indicates the abundance of the cell-surface features to which those dyes are now attached. But at some point, the light signals given off by multiple dyes begin to interfere with one another. It is unlikely that the number of distinct features flow cytometry can measure simultaneously will exceed 20 or so.

The new high-tech, dye-containing particles used by the Stanford team go a step further. They give off not just single-wavelength fluorescent echoes but also more complex fingerprints comprising wavelengths slightly different from the single-color

beams that lasers emit. These patterns, or Raman signals, occur when energy levels of electrons are just barely modified by weak interactions among constituent atoms in the molecule being inspected.

Raman signals are emitted all the time by various molecules, but usually they are too weak to detect. To beef up their strength, the Stanford team employed specialized nanoparticles produced by Intel Corporation, each with its own distinctive signature. Intel has designed more than 100 different so-called COINs, or composite organic-inorganic nanoparticles, that are essentially sandwiches of dye molecules and atoms of metals such as silver, gold, or copper, whose reflective properties amplify a dye molecule's Raman signals while filtering out its inherent fluorescent response. The signals are collected and quantified by a customized, automated microscope.

Dr. Shachaf anticipates being able to demonstrate the simultaneous visualization of 9 or 10 COIN-tagged cellular features in the near future and hopes to bring that number to 20 or 30, a new high, before long. "The technology's capacity may ultimately far exceed that number," she added. Some day it could be used for more than 100 features. Meanwhile, another group outside Stanford, now collaborating with Dr. Nolan's group, has developed a prototypical device that can detect Raman signals in a continuous flow of single cells, analogous to flow cytometry but with higher resolving power, Dr. Shachaf said.

This work, which is detailed in the paper "A novel method for detection of phosphorylation in single cells by surface enhanced Raman scattering (SERS) using composite organic-inorganic nanoparticles (COINs)," was supported by the NCI Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. Investigators from Intel Corporation also participated in this study. An abstract is available at the journal's Web site.

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