New approach to monitoring changes in cellular structure may lead to early detection of cancerous cells

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Researchers have developed a new approach to characterizing and monitoring changes in cellular structure. The new type of single-cell-based assay, developed by researchers at Roswell Park Cancer Institute (RPCI) and the University at Buffalo (UB), may provide a tool for detecting cancerous cells early and monitoring cell-to-cell variations in cancer progression or in response to pharmaceutical drugs.

Dhyan Chandra, PhD, an Associate Professor of Oncology in the Department of Pharmacology & Therapeutics at RPCI, and co-authors conducted a multidisciplinary study with two separate but complementary approaches. Their goal was to define the structural and functional changes at the mitochondrion, an organelle within cells, in response to DNA damage that leads to apoptosis, a form of programmed cell death. Apoptosis is essential for normal tissue function and homeostasis. Research has shown that dysregulated apoptosis is associated with the development of cancer, immune disorders, neurodegeneration and cardiac diseases.

Because identification of apoptotic or diseased cells under physiologic conditions has not been defined, the researchers concluded, there is a need for new approaches that can identify and monitor changing cellular structure during apoptosis. The team used vibrational Raman microspectroscopy, a label-free and noninvasive approach, to probe colon cancer cells at the single-cell level during the progression of

apoptosis.

"Raman microspectroscopy relies on inelastic scattering of monochromatic light by the molecular constituents of the cell sample," notes co-author Paras N. Prasad, PhD, a Distinguished Professor of chemistry, physics, medicine and electrical engineering, Samuel P. Capen Chair of Chemistry and Executive Director of the multidisciplinary Institute for Lasers, Photonics and Biophotonics at UB. "The interaction of light with different types of molecules in cells generates a Raman spectrum, which essentially represents a chemical fingerprint of the interrogated area in cells."

The team compared Raman spectra from mitochondria of individual apoptotic and nonapoptotic cells to monitor overall changes in the molecular content of the mitochondria. They also measured these changes using biochemical methods. Results of the analysis revealed that conformational changes in proteins and transformations in biomolecular composition on mitochondria occur in response to DNA damage, and these changes could represent an apoptosis marker in an individual cell.

"Thus, we defined the previously unknown dynamic correlation of biomolecular composition of mitochondria and apoptosis progression," Dr. Chandra says. "These findings open up a new approach for monitoring the physiological status of individual cells by a noninvasive method."

The researchers observed that in response to the DNA damage, mitochondria accumulate higher levels of DNA and proteins, while the levels of other molecules such as lipids and RNA decrease. In addition, in response to stress, a particular conformation of proteins appears to accumulate on the mitochondria.

"The genesis of cancer involves defects in mitochondria structure and

function, whereas normal cell mitochondria do not have these defects. Our findings provide an opportunity to develop novel tools for detecting cells with defective mitochondria," Dr. Chandra says. "Thus, identification of damaged cells during the early stages of cancer development can have significance in detection and treatment of various types of solid tumors."

This study, entitled, "Transformations of the Macromolecular Landscape at Mitochondria During DNA-Damage-Induced Apoptotic Cell Death," was published online Oct. 9 ahead of print in the journal *Cell Death and Disease*.

More information: "Transformations of the macromolecular landscape at mitochondria during DNA-damage-induced apoptotic cell death." *Cell Death Dis*. 2014 Oct 9;5:e1453. DOI: 10.1038/cddis.2014.405.

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