Cancer Cell Project gets National Cancer Institute Funding

Burke leads a three-campus collaboration that is studying the cancer cell life/death cycle.

April 22, 2015 - A national team of scientists, led by Samueli School professor Peter Burke, is using nanofluidics to peer into the life and death cycle of cancer cells, hoping the information will one day lead to personalized treatment protocols and the development of more effective, cell-targeted pharmaceuticals.

Burke, professor of electrical engineering and computer science, and researchers from Harvard and the University of Pennsylvania recently were awarded nearly $1.2 million from the National Cancer Institute. The grant is funded through the NCI's Innovative Molecular Analysis Technologies program, which supports the development, technical maturation and dissemination of potentially transformative next-generation technologies in cancer research. The collaborators seek to map out pathways of the molecular process in cancer cells – pathways that allow the cells to avoid natural cell death and continue proliferating.

At the heart of the research is a nanofluidic chip, which can manipulate and probe single mitochondria from healthy and cancer cells, allowing them to be tested with libraries of proteins and chemicals – both natural and manufactured – to learn more about why cancer cells respond to signals differently than non-cancerous cells. Researchers will measure the cell life/death decision-making process, using a variety of methods including nanosensors capable of measuring mitochondrial electrical energy.

The mitochondria, often known as the cell's power plants, metabolize sugar to create energy; this energy is stored as a voltage across their surface. But mitochondria have a secondary role: they

regulate the cell-death pathway. Normal cells react to stress by undergoing a process called apoptosis – programmed cell death. In response to certain triggers, the mitochondria form a pore or pores on their surface, spilling out a signaling protein that prompts the cell to self-destruct. When a cell dies, the voltage from the mitochondria shuts down as well. But cancer cells express an abundance of BCL2, a protein that keeps these apoptotic functions suppressed.

By subjecting mitochondria from cancerous tissue to different combinations and concentrations of chemotherapy drugs, and manufactured and natural proteins, researchers hope to learn which unique combinations can overpower the effect of BCL2 cell proteins on apoptosis and force mitochondria to form the pores that lead to cell death.

“Here is the question we’re trying to answer: Why don’t cancer cells die and how does chemotherapy work?” Burke says. “Cancer cells are resistant to the signals that cause them to die. Understanding that process is very important in understanding cancer.”

Researchers do know that two people with the same cancer often react differently to the exact same treatment. Similar tumors can have different properties, causing some cells to depolarize (die) more easily than others. This lab-on-a-chip technology could one day lead to advances in personalized medicine, using test results from specific tumors to create individualized treatment plans, “because not only are people different, but tumors themselves are different,” Burke says.

Current cancer treatment has another well-known drawback; chemotherapy drugs routinely kill healthy cells along with tumors. “This [technology] could help us figure out a way to cause the cancer cells to commit suicide without causing the same reaction in other cells,” according to Burke.

The tiny chip, currently in development, ultimately will contain thousands of ½-micron-wide channels, allowing high-throughput testing. (One-half a micron is 500 nanometers, less than 1/100 the width of a human hair.) Current tumor profiling is still rudimentary; it requires tens of thousands of cells to obtain a small amount of information. The chip being developed in Burke’s lab will have the capability to test single cells or mitochondrion, allowing researchers to get a lot more information from tissue samples much more quickly. According to Burke, a 10,000-cell assay on the chip could yield up to 1 million times more information than current techniques. “We’re going to make that assay thousands of times more powerful by testing not just one or two drugs at a time but thousands of different combinations of drugs or different concentrations.”

Researchers also are hoping to develop on-chip technology that will allow them to understand the biophysical mechanisms that create the formation of the mitochondrial pores. Scientists aren’t sure exactly how the pores form, what their electrical properties are and whether mitochondria produce one pore or multiple pores during apoptosis.

“If we can figure out what is causing the mitochondria to depolarize, we will have a better understanding of why the cancer cell lives or dies,” Burke says. “The technology will help us start asking questions about these metabolic pathways and start answering the questions of why cancer cells don’t die.”

Collaborators on the project include Anthony Letai from Harvard University and Douglas Wallace from University of Pennsylvania.

-- Anna Lynn Spitzer

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