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Survey of Metabolites Finds New Prostate Cancer Marker

Howard Hughes Medical Institute researchers have identified a new biological marker present in the urine of patients with prostate cancer that indicates whether the cancer is progressing and spreading.

In experiments reported in the February 12, 2009, issue of the journal *Nature*, the scientists identified 10 metabolites that become more abundant in prostate cells as cancer progresses. Their studies showed that one of these chemicals, sarcosine, helps prostate cancer cells invade surrounding tissue.

HHMI investigator Arul Chinnaiyan and colleagues at the University of Michigan showed that as prostate cancer develops and progresses, sarcosine levels increase in both tumor cells and urine samples, suggesting that measurements of the metabolite could aid in non-invasively diagnosing the disease. Researchers might also be able to inhibit prostate cancer's spread by designing drugs that manipulate the sarcosine pathway.

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- Arul M. Chinnaiyan

The study is the first to analyze the levels of more than 1,000 different metabolites in human tumors. Scientists know that cells undergo complex changes as cancer develops and progresses to metastatic disease. Chinnaiyan's lab, which has extensively analyzed how genes and proteins in prostate cancer cells reflect these changes, thought that profiling cells' metabolites would offer an even more "holistic picture of the molecular alterations that occur," he said.

"This allows us to have more of a systems perspective of cancer development," he noted. "We are also looking at gene and protein markers, for therapeutic consideration, biomarker consideration, and just understanding the biology. We are not sure yet how it's going to sort out, so

we're being non-discriminatory with what types of technologies we use.”

In the experiments reported in *Nature*, the scientists used mass spectrometry, a technique that identifies chemicals based on the size and electrical charge of their components, to compare the levels of 1,126 metabolites in healthy prostate tissue, clinically localized prostate cancer, and metastatic prostate cancer. Sixty metabolites were present in tumor cells, but not in benign tissue. Of these, there were about 10 molecules whose levels increased dramatically during cancer progression. “This is proof-of-principle that we can identify metabolites, or panels of metabolites, that might be correlated with aggressive prostate cancer versus slower-growing prostate cancer,” Chinnaiyan said.

Having demonstrated that “metabolomic” profiles change in predictable ways as cancer progresses, the group began more focused analyses. “We began to mine the data to look for metabolites that might serve as biomarkers or as therapeutic targets,” Chinnaiyan explained. They chose to focus on sarcosine because it was elevated in clinically localized disease and very highly elevated in metastatic cancer.

They confirmed these dramatic increases in a new set of tissue samples, and also found that there was more sarcosine in the urine of patients with prostate cancer than in healthy individuals.

The team went on to test how sarcosine affected the behavior of cancer cells grown in the laboratory. Adding the chemical to prostate cells or manipulating cells’ biochemical pathways so they produced more sarcosine on their own caused benign prostate cells to become cancerous and invasive. Conversely, shutting down sarcosine production in cancer cells blocked invasion.

“This really told us that sarcosine is involved biologically in some of the processes of a cancer cell,” Chinnaiyan said. The results suggest that drugs that alter sarcosine metabolism might be useful in treating prostate cancer, but Chinnaiyan cautions that these Petri-dish findings still need further validation in animal models.

An important next step, he says, will be to do similar experiments on the other nine potential biomarkers they identified in this study. For reliable diagnosis of aggressive disease, he said, “we need to have panels, not just rely on a single metabolite.”