(From left) The first four authors of the June 24 Cancer Cell study, Barry Taylor, Anuradha Gopalan, Haley Hieronymous, and Nikolaus Schultz.

Summary

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A team of clinicians and computational biologists have compiled the largest catalog to date of genetic alterations that occur in prostate cancer. Their data is now available to other researchers through a public Web site, and may be ripe for translation into more effective diagnostic tests and therapies.

“One of the holy grails of prostate cancer research is to be able to identify which tumors need to be aggressively treated and which don’t,” explained

Charles L. Sawyers, Chair of Memorial Sloan Kettering's Human Oncology and Pathogenesis Program and a senior author of the study, which was published in *Cancer Cell* on June 24. [PubMed Abstract]

In some cancer types, including breast and lung cancer, findings from genome projects have made it possible to classify tumors based on their genetic make-up and to make more informed treatment choices based on such classification. But until recently, genomic research had provided less understanding about the differences that exist among tumors of the prostate — some of which grow so slowly that patients never experience problems, while others are aggressive and lethal.

One reason is that the tumors, which often grow in small masses throughout the prostate, are notoriously difficult to isolate and analyze. In addition, since gene mutations are relatively rare in early prostate cancer, researchers need to examine other types of genomic features to assess whether early-stage tumors will quickly become life-threatening.

A decade ago, the late William L. Gerald (1954-2008), a surgical pathologist at Memorial Sloan Kettering, initiated a collection of high-quality tumor specimens obtained from prostate cancer patients who were treated surgically at Memorial Hospital — all of whom had consented to having their clinical history archived along with samples of their tumors.

In building and exploring this knowledge bank — which today is one of the largest of its kind for prostate cancer research — Dr. Gerald worked closely with a team of surgeons and medical oncologists. The team was led by Peter T. Scardino, Chair of the Department of Surgery. The group also included Victor Reuter, Vice Chair of the Department of Pathology. Later, they were joined by clinical and laboratory scientists led by Dr. Sawyers and Chris Sander, who chairs the Sloan Kettering Institute's Computational Biology Program.

The researchers collected different types of information about genomic alterations in these tumors — including the DNA sequences of cancer-related genes, gene expression patterns, and gene copy numbers. (A cell normally contains two copies of each gene, but cancer cells often have extra or missing copies of some genes.)

When combining this information they discovered that, for some genes, extensive copy-number changes were characteristic of tumors that were destined to advance quickly.

Studies are now under way to explore if copy-number profiling might provide a new way to predict the course of a patient's disease. The findings could lead to the creation of a genetic test to help determine whether or not a patient should be treated, Dr. Sawyers said.

The study has also invigorated hope for the development of new therapies. In analyzing their data, the researchers were able to identify several cellular processes, or pathways, that in many cases might drive prostate cancer progression. And such major pathways are believed to be the most suitable ones to explore as drug targets.

Pathway identification tends to require advanced computer science applications, Dr. Sander explained. "The problem with a disease like prostate cancer is that each tumor has a different genetic profile. So if we simply compare tumor samples gene by gene, very few single-gene common themes emerge," he said, referring to themes in tumor biology that could point the direction for biomarker and therapy development and potentially be exploited in the clinic.

For this reason, he and his colleagues Nikolaus Schultz, Barry Taylor, and Ethan Cerami have developed a method called network analysis, in which a computer sifts through large amounts of genomic data and views it in light of what is known about genes and the way they interact in normal and cancerous cells. There is so much knowledge about the more than 20,000 human genes that "the human brain alone can no longer process all this information," Dr. Sander said, "so use of advanced computer methods in cancer biology is now a necessity."

Pathway analysis revealed, for example, that in nearly all metastatic prostate tumors, and a large fraction of primary ones, a variety of gene alterations had led to activating alterations of the androgen receptor pathway. This observation might help researchers understand why certain types of drugs work in some patients and not in others, and develop more effective treatment strategies.

Dr. Sander noted that a genome project of this scope could not have been achieved without strong teamwork that transcends disciplines, "which is one of the things Memorial Sloan Kettering does best. It was wonderful to see such a diverse group of scientists and clinicians gather every other week to solve these complicated problems," he recalls, "thanks to the initiative William Gerald took."