MedicalXpress

Researchers discover Achilles' heel in lethal form of prostate cancer

November 17 2011

An international team of researchers led by clinicians at Weill Cornell Medical College have discovered a genetic Achilles' heel in an aggressive type of prostate cancer -- a vulnerability they say can be attacked by a targeted drug that is already in clinical trials to treat other types of cancers.

In today's issue of *Cancer Discovery*, the researchers report that the investigational drug had a dramatic response in animal models of neuroendocrine prostate cancer, and so provides the first hope of an effective human therapy for this lethal cancer. While fewer than 2 percent of prostate tumors in men are initially classified as neuroendocrine, many common adenocarcinoma prostate cancers change their biology during hormone therapy and morph into this aggressive subtype.

The study is the largest in-depth analysis of neuroendocrine prostate cancer yet undertaken, and the findings "are very exciting, because our bench-to-bedside approach identified a new molecular target for a subtype of prostate cancer for which a drug is now available," says the study's senior investigator, Dr. Mark A. Rubin, a professor of pathology and laboratory medicine at Weill Cornell Medical College and a pathologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

The finding is especially important because many men are now being treated with new, highly potent androgen suppression therapy, which

these researchers believe will significantly increase the risk of future development of neuroendocrine tumors. Androgen is the fuel that feeds adenocarcinoma prostate cancers -- the most common kind of prostate cancer -- and androgen suppression therapy effectively destroys cancer cells that depend on this hormone. But the treatment does not touch neuroendocrine cells that may have been part of the tumor mix, and those untreatable cells now have room to grow and spread, the researchers say.

Although most of the approximately 30,000 men who die of advanced prostate cancer each year had been treated with androgen suppression therapy, it is impossible to know how many of them developed neuroendocrine tumors because patients are not usually biopsied at that stage in their disease, the researchers say. Studies to define changing biology in prostate cancer are only now starting.

"Still, there is evidence to suggest that androgen suppression results in a more aggressive cancer in a growing number of men, and now, with this study, we may have a way to treat these patients," says the study's lead investigator, Dr. Himisha Beltran, assistant professor of medicine at Weill Cornell Medical College and a medical oncologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

The Weill Cornell researchers undertook the study to see if they could find a way to target neuroendocrine tumors, which is considered an orphan disease among other types of prostate cancer. They used a next-generation sequence analysis to study the transcriptome -- the RNA messages that tumors produce -- of neuroendocrine tumors compared to adenocarcinoma prostate cancers.

A series of analyses using prostate cancer samples gathered by researchers from the U.S. and Europe concluded that the majority of neuroendocrine prostate cancers significantly overexpressed AURKA

and MYCN genes, and 40 percent of these tumors also had extra copies of these genes. Surprisingly, they also found that a smaller subset of prostate adenocarcinomas also overexpressed these genes, and 5 percent had extra copies. "This may represent a high-risk population that could potentially benefit from screening and early intervention," says Dr. Beltran.

The AURKA gene produces aurora A kinase that plays an important role in cell growth, and some studies have suggested it is an oncogene, says Dr. Rubin. Overproduction of AURKA protein has been identified in colon, pancreatic, breast, liver, head and neck cancers, as well as other tumor types. MYCN encodes a transcription factor that is involved in nervous system development and works to turn on other genes. Alterations in the MYCN gene have not previously been seen in prostate cancer.

In neuroendocrine prostate cancer, the AURKA and MYCN mutations need to work together to promote cancer development, Dr. Rubin says. The kind of lethal interaction has also been found in neuroblastoma, a pediatric brain cancer. But the very good news, he adds, is that aurora kinase inhibitors have been developed and are being tested in a variety of cancers.

This study demonstrated that the aurora kinase inhibitor PHA-739358 worked against human neuroendocrine prostate cells in the laboratory, and that it had a dramatic response in animal models of neuroendocrine prostate cancer. It shrank large tumors to very small sizes in a short period of time, compared to untreated mice. There was also significantly enhanced sensitivity of neuroendocrine prostate cancer compared to prostate adenocarcinoma, Dr. Rubin says. While PHA-739358 was studied in prostate cancer without success, the researchers suspect that few of the patients who participated had neuroendocrine prostate tumors . Dr. Beltran is preparing a clinical trial to test an aurora kinase inhibitor

in prostate cancer patients whose tumors contain neuroendocrine cancer cells or similar molecular alterations involving AURKA and MYCN.

"Not only are we eager to test the drug in patients diagnosed with neuroendocrine prostate cancer, we hope to develop biomarkers that can help us screen patients for these cells before the cancer advances," says Dr. Beltran.

Working with the Weill Cornell researchers on the study were researchers from Yale University, the University of British Columbia, the University of Pittsburgh School of Medicine, the University of Michigan, Howard Hughes Medical Institute, and INSERM, a French biomedical research institution.

"This is a great example of team science," Dr. Rubin says. "The study was only possible because a number of investigators from the U.S. and Europe sent us rare samples of this lethal cancer."

"The Prostate Cancer Foundation was pleased to provide support for this research," states Dr. Howard Soule, chief science officer at the Prostate Cancer Foundation. "This work is highly focused on our Foundation goal to eliminate lethal prostate cancer. We congratulate this team for generating findings that will be rapidly translated into patient treatment."

Provided by New York- Presbyterian Hospital