Estrogen helps drive distinct, aggressive form of prostate cancer

May 27 2008

Using a breakthrough technology, researchers led by a Weill Cornell Medical College scientist have pinpointed the hormone estrogen as a key player in about half of all prostate cancers.

Estrogen-linked signaling helps drive a discrete and aggressive form of the disease caused by a chromosomal translocation, which in turn results in the fusion of two genes.

"Fifty percent of prostate cancers harbor a common recurrent gene fusion, and we believe that this confers a more aggressive nature to these tumors," explains study senior author Dr. Mark A. Rubin, professor of pathology and laboratory medicine, and vice chair for experimental pathology at Weill Cornell Medical College. Dr. Rubin is also attending pathologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

"Interfering with this gene fusion -- or its downstream molecular pathways -- will be crucial in the search for drugs that fight the disease. Based on our new data, we now believe that inhibiting estrogen may be one way of doing so," he says.

The findings are published in the May 27 online edition of the Journal of the National Cancer Institute. Dr. Rubin conducted the study while at the Brigham and Women's Hospital and in collaboration with Dr. Todd Golub and other members of the Broad Institute of MIT and Harvard, in Cambridge, Mass. His team is now continuing this line of research at

Weill Cornell.

Dr. Rubin, along with researchers at the University of Michigan, first discovered and described the common fusions between the TMPRSS2 and ETS family member genes subset of prostate cancer in the journal Science in 2005. "The discovery showed that these malignancies occur after an androgen (male hormone)-dependent gene fuses with an oncogene -- a type of gene that causes cancer," he explains.

Experts have long understood that male hormones help spur prostate cancer -- in fact, androgen-deprivation therapy is a first-line treatment against the disease. And yet the disease can progress despite androgen reduction, suggesting that other pathways might be at work.

"So, we wanted to learn more -- what is the genetic and molecular 'fingerprint' of this aggressive subset of prostate tumor"" Dr. Rubin says.

Answering that question required the analysis of 455 prostate cancer samples from trials in Sweden and the United States that were conducted as far back as the mid-1970s.

"These samples were placed in fixative and not frozen, so we needed new methods of retrieving the genetic information," Dr. Rubin says. To do so, his team led by co-lead authors Dr. Sunita Setlur and Dr. Kirsten Mertz developed an innovative technology for effectively "reading" the gene transcription profiles hidden in the samples.

"That led us to perform the largest gene-expression microarray analysis yet conducted in prostate cancer research, amassing information on more than 6,000 genes," Dr. Rubin says. "This allowed us to obtain a robust, 87-gene expression 'signature' that distinguishes fusion-positive TMPRSS2-ERG cancers from other prostate malignancies."

A close analysis of the signature yielded a surprise: that estrogen-dependent molecular pathways appear to play a crucial role in regulating (and encouraging) this aggressive subset of prostate cancer.

While estrogen is typically thought of as a "female" hormone, men produce it as well.

"Now, we show for the first time that this natural estrogen can stimulate the production of the cancer-linked TMPRSS2-ERG transcript, via the estrogen receptor (ER)-alpha and ER-beta. These receptors are found on the surface of some prostate cancer cells," Dr. Rubin explains.

The finding could have implications for prostate cancer research, including drug development. According to Dr. Rubin, "We now believe that agents that dampen estrogen activity (ER-beta antagonists) could inhibit fusion-positive prostate cancers. Alternatively, any intervention that boosts estrogen activity (ER-alpha) might also give a boost to these aggressive malignancies."

Research into just why fusion-positive prostate cancers are so aggressive -- and potential molecular drug targets to help curb that aggression -- will continue under Dr. Rubin's direction at Weill Cornell, in collaboration with members of his group and with computational biologist Dr. Francesca Demichelis.

"The technological achievement of using fixed samples that were up to 30 years old is significant," Dr. Rubin says. "In the future, we hope to explore banked tissues from clinical trials to help understand why they failed. This should lead to insight for designing the next trial."

Source: New York- Presbyterian Hospital