Scientists discover key event in prostate cancer progression

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A study led by researchers at the Ohio State University Comprehensive Cancer Center and Dana-Farber Cancer Institute reveals how late-stage, hormone-independent prostate tumors gain the ability to grow without need of hormones.

The onset of hormone-independent growth marks an advanced and currently incurable stage of prostate cancer.

The study, published in the July 24, 2009, issue of the journal *Cell*, focuses on androgen receptors, molecules located in the nucleus of cells of the prostate gland and other tissues. Male sex hormones - androgens - bind with these receptors to activate genes that control cell growth.

The researchers show that in androgen-independent prostate cancer, androgen receptors are reprogrammed to regulate a group of genes involved in a different, later, phase of cell division, triggering rapid cell growth. They further show that a modification of a chief component of the chromosome is responsible for this reprogramming.

"Some late-phase prostate cancer does not require androgen hormones for tumor growth, but it does require androgen receptors," says first author and co-corresponding author Qianben Wang, assistant professor of molecular and cellular biochemistry and a researcher with the Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute.

"Our study reveals the role of androgen receptors in hormone independent prostate cancer, how they become active in that disease and what genes they regulate to promote tumor growth."

The findings provide a better understanding of prostate cancer and could identify new therapeutic targets and lead to new treatments for this lethal stage of the disease, he says.

Prostate cancer is the most frequently diagnosed cancer in men. An estimated 192,280 new cases are expected in the United States in 2009, along with 27,360 deaths from the disease.

To conduct the study, Wang working with corresponding author Dr. Myles Brown, professor of medicine at Harvard Medical School and Dana-Farber Cancer Institute, and a group of colleagues used hormone-dependent and hormone independent prostate cancer cell lines, gene expression data and tissue from human tumors.

They showed that in hormone-dependent disease, androgen receptors regulate an early phase of cell cycle. In hormone-independent prostate cancer, however, the receptors are reprogrammed to selectively regulate genes involved in actual cell division, that is, the mitotic phase of the cycle.

A gene called UBE2C was a standout among these genes, and increased expression of that gene correlated with progression to the hormone-independent phase.

Furthermore, a chemical change - an epigenetic change - in a histone protein associated with that gene enabled androgen receptors to bind with and activate the gene in hormone-independent prostate cancer.

Finally, they show that over-expression of this gene is necessary for the

growth of the hormone-independent prostate cancer cells.

"Interestingly," Wang says, "the UBE2C gene is also over-expressed in breast, lung, ovary, bladder, thyroid and esophageal cancers, suggesting that our findings could have wide application."

Source: Ohio State University Medical Center