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Researchers find family of 'on switches' that cause prostate cancer

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Researchers at the University of Michigan Comprehensive Cancer Center have discovered how genes turn on the switch that leads to prostate cancer.

The team discovered that pieces of two chromosomes can trade places with each other and cause two genes to fuse together. The fused genes then override the “off” switch that keeps cells from growing uncontrollably, causing prostate cancer to develop.

By testing these gene fusions in mice and in cell cultures, the researchers showed that the fusions are what cause prostate cancer to develop. But it’s not just one set of genes that fuse. The researchers found that any one of several in a family of genes can become scrambled and fuse. Results of the study appear in the Aug. 2 issue of *Nature*.

“Each of these switches, or gene fusions, represent different molecular subtypes. This tells us there’s not just one type of prostate cancer. It’s a more complex disease and potentially needs to be treated differently in each patient,” says lead study author Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology, a new U-M center whose goal is to translate research into real world practice.

The gene fusion research is the centerpiece project of the new center. In the current study, researchers found one of several abnormal gene fusions in the prostate cancer tissue samples they tested. In 2005, the researchers identified a prostate-specific gene called TMPRSS2, which

fuses with either ERG or ETV1, two genes known to be involved in several types of cancer.

The Nature paper reports on five additional genes that fuse with ERG or ETV1 to cause prostate cancer. Gene fusions were involved in 60 percent to 70 percent of the prostate cancer cell lines the researchers looked at. The genes involved are all controlled by a different mechanism. For example, four of the genes are regulated by androgen, a male sex hormone known to fuel prostate cancer. Androgen deprivation is a common therapy for prostate cancer.

Knowing which gene fusion is involved in an individual patient's tumor could impact treatment options. If an androgen-regulated gene is involved, androgen therapy would be appropriate. But if the gene fusion involves a gene that represses androgen, the anti-androgen therapy could encourage the cancer's growth. This may also explain why androgen treatment is not effective for some prostate cancers.

"Typing someone's prostate cancer by gene fusion can affect the treatment given. We would not want to give androgen to someone whose prostate cancer gene fusion is not regulated by androgen," says Chinnaiyan, who is the S.P. Hicks Collegiate Professor of Pathology at the U-M Medical School.

Rearrangements in chromosomes and fused genes are known to play a role in blood cell cancers like leukemia and lymphoma, and in Ewing's sarcoma. A fused gene combination that plays a role in chronic myelogenous leukemia led researchers to develop the drug Gleevec, which has dramatically improved survival rates for that disease.

Chinnaiyan believes the prostate gene fusions will eventually lead to similar treatments for prostate cancer.

“More immediately, we hope to develop tests for diagnosis or prognosis. But long-term, we hope this will lead to better therapies to treat prostate cancer. The key challenge is to find a drug that would go after this gene fusion,” Chinnaiyan says.

The gene fusion technology has been licensed to San Diego-based Gen-Probe Inc., which is working on a screening tool to detect gene fusions in urine. The tool could one day supplement or replace the prostate specific antigen, or PSA, test currently used to screen for prostate cancer.

The idea of translating laboratory research findings into a test or treatment that will impact patients is central to the new Michigan Center for Translational Pathology. The center brings together experts in genomics, proteomics and bioinformatics to look at common patterns and potential targets in cancer and other diseases. This is the first center of its kind in the nation in that it is associated with one of 39 National Cancer Institute-designated “comprehensive” cancer centers, a premier medical school and a large health system with both clinicians and patients.

The center’s goal is to study the genes, proteins and other markers on cells to develop new diagnostic tests or screening tools as well as targeted treatments for cancer and other diseases, with the key being to translate these laboratory discoveries into clinical applications.

Chinnaiyan and his team have received numerous awards and honors, including the American Association for Cancer Research Team Science Award for their previously published work on gene fusions, and the Specialized Program of Research Excellence Outstanding Investigator award. The new Center for Translational Pathology supported in part by the Prostate Cancer Foundation, which has offered to match up to $1 million dollars in donations to support work related to developing therapies against prostate cancer gene fusions at the university.

“Mapping of the human genome was only the beginning. Equipped with the comprehensive analysis of the human genome, we can now systematically examine the blueprint of disease at the molecular level. This essential knowledge may lead to better diagnostic tests and promising new treatments for cancer, cardiovascular disease, diabetes and other illnesses,” Chinnaiyan says.

Source: University of Michigan