Periodic bursts of genetic mutations drive prostate cancer

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Cancer is typically thought to develop after genes gradually mutate over time, finally overwhelming the ability of a cell to control growth. But a new closer look at genomes in prostate cancer by an international team of researchers reveals that, in fact, genetic mutations occur in abrupt, periodic bursts, causing complex, large scale reshuffling of DNA driving the development of prostate cancer.

In the April 25 issue of *Cell*, the scientists, led by researchers from Weill Cornell Medical College, the Broad Institute, Dana-Farber Cancer Institute and the University of Trento in Italy, dub this process "punctuated cancer evolution," akin to the theory of human evolution that states changes in a species occur in abrupt intervals. After discovering how DNA abnormalities arise in a highly interdependent manner, the researchers named these periodic disruptions in cancer cells that lead to complex genome restructuring "chromoplexy."

"We believe chromoplexy occurs in the majority of prostate cancers, and these DNA shuffling events appear to simultaneously inactivate genes that could help protect against cancer," says the study's co-lead investigator Dr. Mark Rubin, who is director of the recently-established Institute for Precision Medicine at Weill Cornell Medical College and NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

"Knowing what actually happens over time to the genome in cancer may lead to more accurate diagnosis of disease and, hopefully, more effective treatment in the future," says Dr. Rubin, also the Homer T. Hirst III

Professor of Oncology, professor of pathology and laboratory medicine and professor of pathology in urology at Weill Cornell and a pathologist at NewYork-Presbyterian/Weill Cornell. "Our findings represent a new way to think about cancer genomics as well as treatment in prostate and, potentially, other cancers."

The discovery of "chromoplexy" came after the research team worked collaboratively to sequence the entire genomes of 57 prostate tumors and compare those findings to sequences in matched normal tissue.

Co-lead investigator Dr. Levi Garraway, of the Broad Institute and Dana-Farber Cancer Institute, and his collaborators then tracked how genetic alterations accumulated during cancer development and progression. They used advanced computer techniques to identify periodic bursts of genetic derangements.

"We have, for the first time, mapped the genetic landscape of prostate cancer as it changes over time," says Dr. Garraway, a senior associate member of the Broad Institute and associate professor at the Dana–Farber Cancer Institute and Harvard Medical School. "The complex genomic restructuring we discovered, which occurs at discrete times during tumor development, is a unique and important model of carcinogenesis which likely has relevance for other tumor types."

Co-senior author Dr. Francesca Demichelis, assistant professor at the Centre for Integrative Biology at the University of Trento who also serves as adjunct assistant professor of computational biomedicine at Weill Cornell, worked with her collaborators to understand how widespread the DNA mutations and alterations seen in the tumors were across the cancer samples, and what that might mean in terms of cancer progression and, potentially, treatment. "Information about what alterations are common, and which aren't, will most likely help guide us in terms of cancer drug use and patient response," says Dr. Demichelis.

The researchers also report that future targeted cancer therapy may depend on identifying complex sets of genetic mutations and rearrangements in each patient.

"Every cancer patient may have individual patterns of genetic dysfunction that will need to be understood in order to provide precise treatment. Multiple drugs may be needed to shut down these genetic derangements," says Dr. Rubin. "Providing those tests now on every patient isn't possible, but our study suggests that punctuated cancer evolution may occur to provide a subset of genes that offer a selective advantage for tumor growth. If that is true, we may be able to zero in on a limited number of genetic drivers responsible for an individual's prostate cancer."

Astonishing Degree of Genetic Alterations

The collaborators have been working together for a number of years exploring and mapping the prostate cancer genome. They believe that structural genomic alterations are key to prostate cancer development and progression, and their approach has been to model those changes and tease apart the significance of those alterations.

This study sequenced 57 prostate cancer genomes as well as the entire genomes of matched normal tissue. Researchers revealed an astonishing number of genetic alterations in the prostate cancer cells—356,136 base-pair mutations and 5,596 rearrangements that were absent from normal DNA. Of those rearrangements, 113 were validated by re-sequencing and other methods.

"We saw wholesale rearrangements of chromosomes—the cutting up and retying of chromosomes—mutations we have never seen on that scale," Dr. Garraway says. "Our research teams then charted a path of oncogenic events that appeared to drive prostate cancer."

Using advanced computer techniques that modeled the genomic rearrangements and copy number alterations, the scientists at the Broad Institute inferred that the chromosomal disarray in a typical tumor might accumulate over a handful of discrete events during tumor development.

"The rearrangement of chromosomes can coordinately affect specific genes, which provides a selective advantage for cancer growth," according to Dr. Garraway.

"Chromoplexy is a common process by which geographically-distant genomic regions may be disrupted at once, in a coordinated fashion," says Dr. Rubin. "The unifying feature is that these alterations seem to occur in a sequential, punctuated pattern which is designed to eliminate cancer-fighting genes. This suggests that genes that are active at the end of these events may drive progression of the cancer."

"This study represents a wonderful example of a team science that embraces multidisciplinary competencies," says Dr. Demichelis.

The study required the development of special computational tools to go beyond the pure detection—presence or absence—of any particular aberration, and to quantify the dosage of the mutation; meaning, how many tumor cells have that specific mutation in the patient's tumor.

"The approach developed in my laboratory takes advantage of the genetic information of each individual and classifies every aberration as homogenous or heterogeneous across the tumor cells," Dr. Demichelis says. "This classification allows us then to chart the order in which mutations occur and to learn how far the tumor is in its progression. It suggests to us that patients with heterogeneous aberrations may not respond as effectively to a drug as patients with homogenous alterations."

"The punctuated changes we see occur in a single cycle of cell growth, and we believe this leads to tumor cells that have a growth advantage," says Dr. Rubin. "This new model of cancer growth tells us that cells gain an advantage mutating multiple genes simultaneously as opposed to gradually."

"These are exciting findings in a field of prostate cancer genomics that our research team's collaboration has redefined. We have made a lot of progress, but we have much more work to do," adds Dr. Rubin.

Provided by Weill Cornell Medical College