Autopsy study links prostate cancer to single rogue cell

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that's all it takes to begin a series of events that lead to metastatic cancer. Now, Johns Hopkins experts have tracked how the cancer process began in 33 men with prostate cancer who died of the disease. Culling information from autopsies, their study points to a set of genetic defects in a single cell that are different for each person's cancer.

"These were not your average autopsies," says pathologist G. Steven Bova, M.D., assistant professor of pathology at Johns Hopkins. "We dissected every bit of tumor - in the primary and metastatic sites - and recorded exactly where each piece of tissue came from, analyzed it, and databased the findings." In total, Bova estimates that he and his colleagues examined 150,000 slides and 30,000 blocks of tissue.

The study took 14 years to complete, and part of the challenge was in finding men living with prostate cancer who would agree to have their body autopsied immediately after they died. "Many of the men were motivated to join the study in hopes of leaving some legacy that might lead to cures for this cancer," says Bova, who holds secondary appointments in the departments of pathology, genetic medicine, health sciences informatics, oncology, and urology at Johns Hopkins.

"Much is unclear and appears chaotic about how cancer spreads, but analyzing genetic markers allows us to trace its roots backward, somewhat like ancestry," says Bova. Findings from the study were published online April 12 in *Nature Medicine*.

Clues to finding the genetic culprit for cancer spread are hidden in the changes that occur in a cell's DNA, the alphabetical code made up of chemicals that guide the everyday life of a cell. Cancers are caused by alterations in DNA code that occur in a variety of ways: making errors in the nucleotide alphabet through mutations, changing the balance of chemicals attached to the on/off switches of genes, and altering the number of gene copies in a cell. When the number of gene copies is disrupted in a cell beyond the customary two copies inherited from each parent, a gene's function can be damaged. This process, called copy number variation, can set the stage for unchecked cell growth and spread, a hallmark of cancer.

For this study, the investigators scanned genes spanning the whole genome in the autopsy samples looking for areas of copy number variation. They did this by attaching the DNA to special silicon chips, and then photographed them with a computer program that produces a report with varying colors representing the amount of DNA in the sample.

The scientists compared the patterns of gains and losses in tissue samples from multiple metastatic sites in 29 of the men. Unique copy number changes were identified, as well as ones that were shared between multiple metastatic sites in each man and with other men in the study.

For example, in several men, the investigators found cells in different areas of metastasis that contained missing chunks of DNA in one common region of the genome. The exact location of the DNA loss was different for each man, but all occurred in the same DNA region. "Each person has a different set of defects that contributes to the cancer," explains Bova.

Metastatic sites develop from cancer cells that break off of the primary cancer. If cancer cells at more than one metastatic site carry a common

set of nonrandom genetic defects, it is likely that these cells are derived from a single parent cell, says Bova. Tissue samples from 14 of the 33 men were studied at the highest available resolution, and all showed common genetic patterns across metastatic sites, suggesting a single cell source for their cancer.

Bova says that future studies will help determine whether the common set of changes shared by the various metastatic sites arose in a single "big bang" in the prostate or if the changes accumulated more slowly over time.

Bova says that such autopsy studies of metastatic cancer can provide a molecular catalogue of cellular defects specific to individuals and general groups. The findings, he says, could help narrow the focus of research and guide personalized cancer therapy.

More information: *Nature Medicine*: www.nature.com/nm/index.html

Source: Johns Hopkins Medical Institutions