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A New Ground Zero for Prostate Cancer

A type of prostate cell that has been largely ignored by cancer researchers can, in fact, trigger malignant prostate cancer, according to new studies by Howard Hughes Medical Institute (HHMI) scientists and their colleagues.

HHMI researcher Owen N. Witte and his colleagues at the University of California, Los Angeles (UCLA) found that the somewhat overlooked prostate basal cell can spawn tumors in the prostate gland. Their studies, which were unveiled in the July 30, 2010 issue of *Science*, now provide researchers with a new tool for exploring the genetic changes that lead to prostate cancer. Witte said the advance may help in developing new treatments for the disease, which causes some 32,000 deaths in the United States annually.

"We've defined one cell type as an originator of prostate cancer," says Witte, who led the research published in *Science*. "Now we can use that knowledge to find genetic pathways that can be attacked therapeutically to control the disease."

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Two main cell types comprise the prostate, which is a gland filled with a network of small tubules. Luminal cells coat the inner layer of the tubules and produce fluids and proteins that aid reproduction – the prostate's main purpose. The second type of cell -- called basal cells -- builds the outside layer, or base, of the tubules.

Researchers have long thought that luminal cells give rise to prostate cancer because prostate tumor cells have the same large, columnar shape as luminal

cells when viewed under a microscope. But previous research from Witte's laboratory showed that, in mice, basal cells, not luminal cells, acquired the genetic damage required to turn cancerous. To extend these results to humans, Witte and colleagues at UCLA developed new techniques to study human prostate tissue and its propensity to cause cancer.

Over a period of several years, the team first identified a series of unique cell surface markers that help researchers distinguish luminal cells from basal cells. They then used these markers to separate the two cell types in samples of human prostate tissue. Patients undergoing prostate cancer surgery agreed to donate the tissue for research studies. In those operations, a surgeon typically removes healthy tissue along with the cancer. The tissue from those operations was given to Witte's team to provide the material they needed for their studies.

After separating luminal cells from basal cells, the researchers prodded all of the cells to become cancerous by introducing three genes known to promote prostate cancer. A virus was used to deliver the genes -- called *AKT*, *ERG*, and *AR* -- into luminal cells and basal cells.

The researchers then separately engrafted the transformed luminal cells and the transformed basal cells into mice. After 16 weeks, none of the luminal grafts had formed tumors. In the meantime, though, the basal cell grafts had gone through three stages: They had grown into prostate-like tubules, transformed into damaged pre-cancerous cells, and then turned malignant and formed tumors. Tellingly, when examined by a pathologist, these tumors looked identical to human prostate tumors, said Andrew Goldstein, a Ph.D. student in Witte's lab and first author on the *Science* paper.

"In our experimental model, basal cells show the ability to form the disease that looks like what we see in humans," says Goldstein. "We feel very confident that we have recreated something that strongly resembles human prostate cancer. We conclude that basal cells may be a source of the disease in humans."

The engrafted basal cells -- after turning cancerous -- also looked very much like luminal cells, as in clinical tumor samples. Witte says that this suggests that on their way to becoming cancerous, basal cells grow into more luminal-like cells. This makes sense, he notes, because the engrafted human basal cells also acted like prostate stem cells, growing into prostate tubules with luminal cells on the inside.

The research adds to previous evidence showing that tissue-specific stem cells possess a dangerous propensity to grow out of control into cancer, says Witte. "There's lots of data that suggest that tissue stem cells -- which have the ability to self-renew and to differentiate into other cells -- are at the root of many organ-specific cancers. Now we've found something similar with prostate cancer." Witte says he is now searching for specific subtypes of

stem-like basal cells that are the bad actors in this new model of prostate cancer.

Finding the cancer cell of origin has already paid dividends in Witte's career. Some two decades ago, he helped discover that the cells that grow out of control in chronic myelogenous leukemia (CML) are blood-forming stem cells. A close examination of the genetic events that triggered cancer in those cells pointed to two broken genes that fused to create a new gene called *BCR-ABL*. In 2000, the Food and Drug Administration approved Gleevec, a drug that inhibits the *BCR-ABL* fusion gene product. Gleevec has since shown remarkable potency against CML.

While it may be years before researchers will know whether the new model developed by Witte and colleagues might have a similar impact on prostate cancer, they can at least now begin to use the model to test suspected prostate cancer oncogenes systematically and in a more efficient manner. Any gene can be inserted into the viruses that infect the human basal cells, so researchers can test a large number of genes with the goal of finding new targets for drug development.