Scientists pinpoint a cell-of-origin for human prostate cancer

29 July 2010

UCLA scientists have identified for the first time a cell-of-origin for human prostate cancer, a discovery that could result in better predictive and diagnostics tools and the development of new and more effective targeted treatments for the disease.

For the first time, UCLA scientists have stumbled upon a cell-of-origin for human prostate cancer. This a groundbreaking discovery that could potentially result in better predictive and diagnostic tools as well as the development of more effective treatments for the disease.

From UCLA's Jonsson Comprehensive Cancer Center, the researchers proved that basal cells found in the benign prostate tissue in mice, have the potential to become prostate cancer in those with suppressed immune systems. This is a finding that bucks all conventional wisdom. "It had been widely believed that luminal cells found in the prostate were the culprits behind prostate cancer because the resulting malignancies closely resembled luminal cells," said Dr. Owen Witte, a Jonsson Cancer Center senior author, director of the UCLA Broad Stem Cell Research Center and Howard Hughes Medical Institute Investigator. "Certainly the dominant thought is that human prostate cancer arose from the luminal cells because the cancers had more features resembling luminal cells." But we were able to start with a basal cell and induce human prostate cancer and now, as we go forward, this gives us a place to look in understanding the sequence of genetic events that initiates prostate cancer and defining the cell signaling pathways that may be at work fueling the malignancy, helping us to potentially uncover new targets for therapy."

The study will appear in the peer-reviewed July 30, 2010 journal of *Science*.

"The researchers took healthy tissue from prostate biopsies and separated the cells based on their surface marker expression into groups of luminal cells and groups of basal cells," said Andrew Goldstein, a UCLA graduate student and first author of the study. "Using viral vectors as vehicles, they then expressed altered genes known to cause cancer into both cell populations and placed the cells in mice to see which developed cancer. Because of the widespread belief that luminal cells were the root of human prostate cancer, it would have been those cells examined and targeted to treat the disease. This study tells us that basal cells play an important role in the prostate cancer development process and should be an additional focus of targeted therapies."

"In normal prostate tissue, basal cells have a more stem cell-like function," Goldstein added, "meaning they proliferate more to re-grow human prostate tissue. Luminal cells don't proliferate as much, but rather produce major proteins that are important for reproduction." Witte and Goldstein plan to study the cancer-causing basal cells gone awry, to uncover the mechanisms resulting in malignancy.

"Currently, there is a dearth of knowledge about how prostate cancer develops to treat it effectively in a targeted way, as Herceptin targets an out-of-control production of growth factor receptors in breast cancer cells. The major targeted therapy used for prostate cancer is directed at the androgen receptor and it is not always effective," Witte said.

The new human-in-mouse model system created in the study - implanting healthy human prostate tissue, in mice, that will induce cancer, instead of implanting already cancerous tissue - can now be used to evaluate the effectiveness of new types of therapeutics. By using defined genetic events to activate specific signaling pathways, researchers can more easily compare therapeutic efficiency. The new prototype, by deconstructing tissue then reconstructing it, will aid in analyzing how cells change during cancer progression.

"There are very few examples of taking benign cells

and turning them into cancer experimentally," Goldstein said. "We usually study cancer cell lines created from malignant tumors. This study resulted in the creation of a novel model system that is highly adaptable, such that we can test any cellular pathway and its interactions with other genes known to induce cancer, and we can start with any type of cell as long as it can be reproducibly purified."

Unlike the cancer cell lines used in other work, Witte and Goldstein know the "history" of the cells that became cancer.

"We know those cells are malignant, but we don't know how they got there," Goldstein said. "By starting with healthy cells and turning them into cancer, we can study the cancer development process. If we understand where the cancer comes from, we may be able to develop better predictive and diagnostic tools. If we had better predictive tools, we could look earlier in the process of cancer development and find markers that are better than the current PSA test at catching disease early, when it is more treatable."

"Rising PSA levels can indicate the presence of cancer that is already developing in the prostate. However, now that it is known that basal cells are one root of human prostate cancers, scientists can study pre-malignant basal cells and uncover what they express that the healthy ones don't, perhaps revealing a new marker for early detection," Goldstein said. "Also, a therapy directed at the pre-malignant basal cells about to become malignant could provide a way to prevent the cancer before it becomes dangerous."

More than 217,000 men will be diagnosed with prostate cancer this year alone. Of those, more than 32,000 will die from their disease.

Source: University of California - Los Angeles