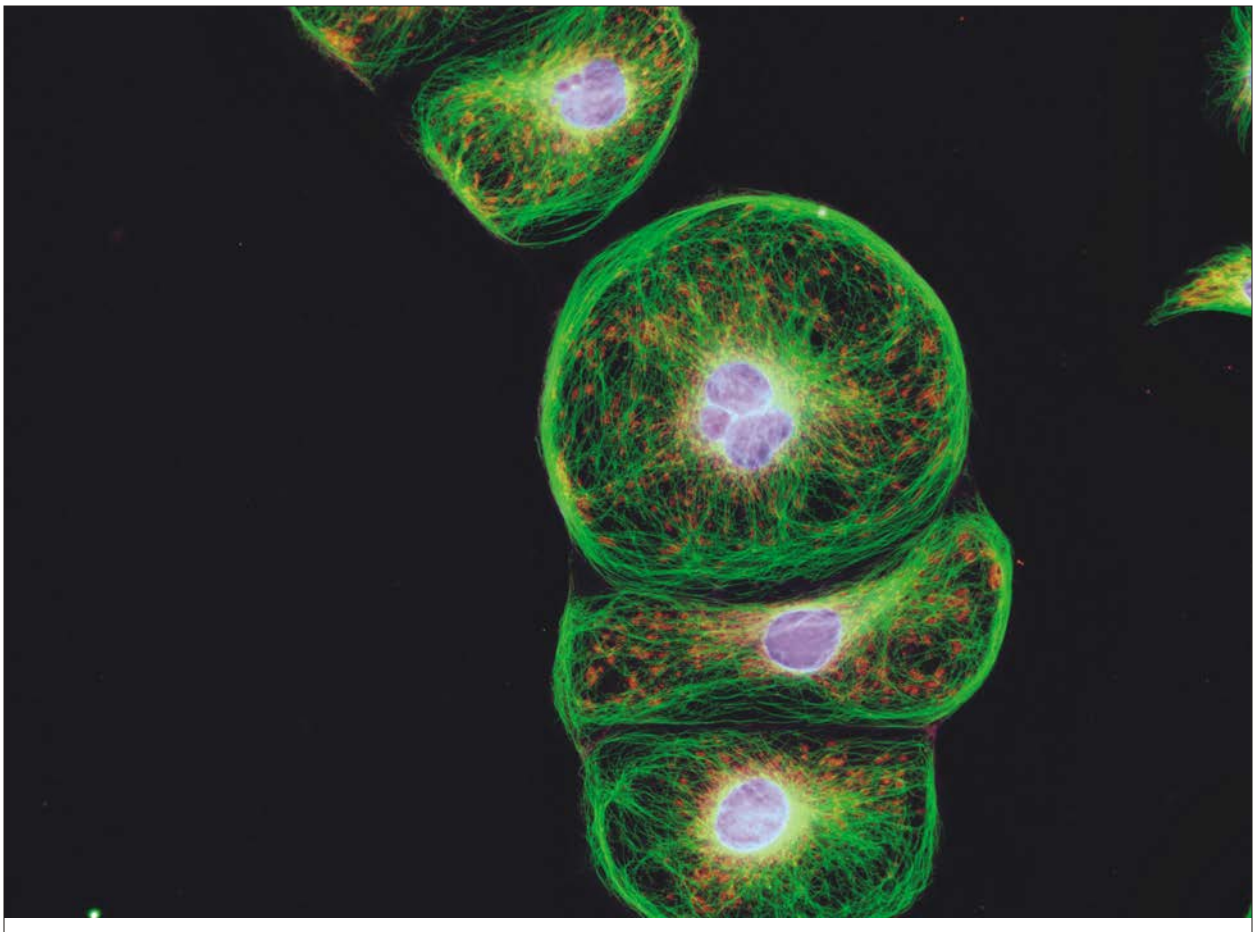

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Scientists Discover Mechanism That Turns Healthy Cells Into Prostate Cancer Cells

A protein that is crucial for regulating the self-renewal of normal prostate stem cells, needed to repair injured cells or restore normal cells killed by hormone withdrawal therapy for cancer, also aids the transformation of healthy cells into prostate cancer cells, researchers at UCLA have found.

The findings, by researchers with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, may have important implications for controlling cancer growth and progression.

Done in primary cells and in animal models, the findings from the three-year study appear Dec. 2, 2010 in the early online edition of the peer-reviewed journal Cell Stem Cell.

The protein, called Bmi-1, is often up-regulated in prostate cancer, has been associated with higher grade cancers and is predictive of poor prognosis, according to previous studies. However, its functional roles in prostate stem cell maintenance and prostate cancer have been unclear, said Dr. Owen Witte, who is Director of the Broad Stem Cell Research Center, a Howard Hughes Medical Institute Investigator and Senior Author of the study.

A study of loss and gain of function in prostate stem cells indicated that Bmi-1 expression was required for self-renewal activity and maintenance of prostate stem cells with highly proliferative abilities. Loss of Bmi-1 expression blocks the self-renewal activity, protecting prostate cells from developing abnormal growth changes which can lead to cancer.

More importantly, Bmi-1 inhibition slowed the growth of an aggressive form of prostate cancer in animal models, in which the PTEN tumor suppressor gene was removed allowing the cancer to run wild, Witte said.

"We conclude by these results that Bmi-1 is a crucial regulator of self-renewal in adult prostate cells and plays important roles in prostate cancer initiation and progression," Witte said. "It was encouraging to see that inhibiting this protein slows the growth of even a very aggressive prostate cancer, because that could give us new ways to attack this disease."

UCLA stem cell researchers have been studying the mechanisms of prostate stem cells for years on the theory that the mechanism that gives the cells their unique ability to self-renew somehow gets high jacked by cancer cells, allowing the malignant cells to grow and spread. If the mechanism for self-renewal could be understood, researchers could find a way to interrupt it once it is taken over by the cancer cells, Witte said.

Rita Lukacs, a doctoral student in Witte's laboratory and first author of the study, found that Bmi-1 inhibition also stops excessive self-renewal driven by other pathways. This suggests that the Bmi-1 pathway may be dominant to other genetic controls that affect the cancer phenotype.

"Prostate cancer can be initiated by so many different mutations, if we can find a key regulator of self-renewal, we can partially control the growth of the cancer no matter what the mutation is," Lukacs said. "We're attacking the process that allows the cancer cells to grow indefinitely. This provides us an alternate way of attacking the cancer by going to the core mechanism for cancer cell self-renewal and proliferation."

Witte said future work will be centered on searching for methods to control these pathways in human prostate cancer cells.

Prostate cancer is the most frequently diagnosed non-skin cancer and the second most common cause of cancer-related deaths in men. This year alone, more than 277,000 men in the United States will be diagnosed with prostate cancer. Of those, 32,000 men will die from the disease.

This study was funded by the California Institute for Regenerative Medicine, Howard Hughes Medical Institute, Prostate Cancer Foundation, Ovarian Cancer Research Fund, a Stewart and Lynda Resnick Prostate Cancer Foundation Grant and a Stein/Oppenheimer Clinical Translational Seed Grant.