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Media contacts:

Vanessa Wasta
Johns Hopkins Kimmel Cancer Center
410-955-1287
wastava@jhmi.edu

Jennifer Ryan
The Cancer Institute of New Jersey
732-235-9891
ryanje@umdnj.edu

PREVENT PROSTATE CANCER WITH ANTIOXIDANTS? GENE PATHWAY MAY REVEAL MORE CLUES

September 15, 2005 – Scientists from Maryland and New Jersey have identified a molecular pathway in mice that makes prostate cells vulnerable to cancer-causing oxygen damage. The pathway, which is also involved in human prostate cancer, may help determine how and whether antioxidants, such as certain vitamins or their products that reverse the damage, can prevent prostate cancer.

The researchers, from Johns Hopkins Kimmel Cancer Center and The Cancer Institute of New Jersey, found that when the tumor suppressor gene Nkx3.1 malfunctions, prostate cells lose the ability to protect themselves from oxygen damage. Results of the new studies are in the August issue of the journal *Cancer Research*.

“Normally, cells with functioning Nkx3.1 seem to process oxidative free radicals appropriately,” says Theodore L. DeWeese, M.D., a co-author of the study and director of the Department of Radiation Oncology & Molecular Radiation Sciences at Hopkins. “But cells with faulty Nkx3.1 genes cannot manage oxidative injury. Then, their DNA gets damaged, and that leads to other mutations that in turn can bring about cancer.”

The researchers specifically found that a key role of Nkx3.1 is to prevent oxidative damage by regulating the expression of other genes. Oxygen causes cellular degeneration through so-called oxidative free radicals --- highly reactive atoms with an unpaired electron that can rip through cells like a bullet. Free radicals are produced as a result of normal body metabolism, and are widely known to be intimately involved in aging, as well as cancer development.

“Our findings provide new insights regarding the relationship between loss of protection against oxidative stress and the initiation of prostate cancer,” adds Cory Abate-Shen, Ph.D.,

senior study author and professor of medicine and neuroscience, member at the Center for Biotechnology and Medicine at UMDNJ-Robert Wood Johnson Medical School. “One key finding is that defects in the oxidative response pathway occur early in prostate cancer development.” Abate-Shen also is co-director of the Prostate Cancer Program at The Cancer Institute of New Jersey.

For the study, the researchers used a sophisticated computer technique called gene expression profiling to compare in-depth the genetic makeup of mice whose Nkx3.1 gene was disrupted with that of normal mice. The method takes all DNA from the cells and allows scientists to look for aberrations. DeWeese likens it to studying thousands of pages of an encyclopedia simultaneously; trying to identify what pages may have been altered.

They observed that mice with malfunctioning Nkx3.1 incorrectly expressed 638 genes, including those that created a significant reduction in some antioxidant enzymes vital to oxidative damage prevention. These alterations occurred in mice as early as four months of age – well before cellular changes are visible in the mouse prostate. The mutant mice also displayed a fivefold increase in the amount of a chemical marker of cancer-related DNA damage, called 8-hydroxy-2'-deoxyguanosine.

Further investigation showed that the progression to prostate cancer as it occurs in mice lacking Nkx3.1 and another tumor suppressor, Pten, correlated with additional deregulation of antioxidants and more profound accumulations of oxidative damage to DNA and protein.

“Mice with defective Nkx3.1 provide a valuable tool for preclinical studies to test whether antioxidants might be useful for prostate cancer prevention,” Abate-Shen says and continuing studies will test antioxidants or other agents on the altered mice.

Prostate cancer is the most commonly diagnosed cancer in men and ranks second to lung cancer as the leading cause of cancer death among American men. More than 232,000 cases of prostate cancer are diagnosed and treated annually in the United States, and close to 30,000 men die each year of the disease. Most men over the age of 50 will have some experience with prostate disease -- with either an enlarged prostate or cancer.

The study was supported by the National Institutes of Health. Co-authors were Xuesong Ouyang of UMDNJ-Robert Wood Johnson Medical School, and William G. Nelson of Hopkins.

Links:

Johns Hopkins Department of Radiation Oncology and Molecular Radiation Sciences

<http://www.radonc.jhmi.edu/>

Johns Hopkins Kimmel Cancer Center

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The Cancer Institute of New Jersey

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