WS1-3-5

A Prostate Cancer Model by the Prostate Specific Deletion of PTEN

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[Introduction and Object] The tumor suppressor gene MMAC/PTEN located on chromosome 10q23.3 is frequently inactivated in a variety of tumors such as prostate cancer and has a dual phosphatase activity in the phosphatidylinositol 3-kinase signal pathway and inhibits Akt activation, a serine-threonine kinase which was involved in proliferative and anti-apoptotic pathways. We generated PTEN conditional gene targeting in the mouse prostate cancer model and analyzed its role in prostate carcinogenesis. [Methods] Based on the Cre/loxP system, we established a PTEN specific deletion in the mouse prostate by crossbreeding PSA-Cre transgenic mice with PTEN-loxP/loxP mice and generated a heterogenic PTEN knock-out mouse (PSA-Cre, PTEN-loxP/loxP) and a homogenic PTEN knock-out mouse (PSA-Cre, PTEN-loxP/loxP). We castrated the mice and examined the histopathological analysis. PIN lesions were observed in the heterogenic PTEN knock-out mice aged from 3 to 9 months (60%, 6/10) and 10 to 14 months (26%, 5/19), furthermore, 53% (10 of 19) mice demonstrated prostate carcinoma, 5% (1 of 19) of which had lung metastasis. Homogenic PTEN knock-out mice exhibited PIN lesions (27%, 3/11), and prostate carcinoma (27%, 3/11) at 2 months. However, at more than 3 months, 94% (30 of 32) mice showed prostate carcinoma lesions and at 10 months, 20% (2 of 10) mice had lung metastasis. Prostate cancer tissues demonstrated an up-regulation of phospho-Akt as well as positive expression of androgen receptor. Homogenic PTEN knock-out mice still exhibited prostate cancer after castration but had decreased expression of androgen receptor. [Conclusions] This model serves as effective tool for the study of prostate carcinogenesis. Furthermore, decrease of androgen receptor may have an association to androgen independent prostate cancer.

WS1-3-6

Is Oxidative Stress Associated with Prostate Cancer Risk?

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We reported at AUA 2007 that MnSOD AA genotype was associated with prostate cancer (PCA) as a function of NAT genotype and smoking status. The purpose is to investigate whether there is an association between the genotype of manganese superoxide dismutase (MnSOD) and N-acetyltransferase (NAT), smoking and PCA. Although neither the genotype of NAT1 or NAT2 nor smoking is associated with prostate cancer, the association of MnSOD AA and PCA is only found in those who had a rapid NAT1 genotype or those who had a history of smoking. This association is greatly increased in those who had a rapid NAT1 genotype and who also had smoked. Since MnSOD is involved in the metabolism of reactive oxygen species (ROS), which is invariably produced during prostatitis, our results suggest that oxidative stress may play a role in the carcinogenesis of the prostate in those who smoked and have a rapid NAT1 genotype. However our study had several limitations. Control subjects did not undergo biopsies to exclude PCA. This is an important aspect of verification bias that is inherent in most case-control studies, because even a negative prostate biopsy could not conclusively rule out early PCA. As have been reported most recently by one of our authors, 8 significant PCAs were present in 91 autopsies who had not previously been diagnosed with PCA and had a PSA level less than 4 ng/ml. Therefore we are now studying MnSOD polymorphism in autopsy prostate. On the other hand, mitochondria have been known to generate significant amounts of hydrogen peroxide. MnSOD is present in the mitochondria and plays an important role in protection from ROS-mediated DNA damage. We hypothesized that the increase in oxidative stress associated with carcinogenesis in individuals with chronic prostatitis might result in mutation of mtDNA. Therefore we attempt to sequence the mitochondrial genome of cancersous and noncancersous regions of the prostate of individuals with PCA and compared the sites and frequencies of mutations with those detected in normal prostate.