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Microarray Analysis of Prostatic Intraepithelial Neoplasia

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Prostate cancer is the most common male cancer in western countries, yet little is known about its initiation and development. 10-20% of the patients present already with bone metastasis at the time of diagnosis. We hypothesize that PIN expresses genes which distinguish it from normal and carcinomatous epithelia; the gene profile may give hints to carcinogenesis in the prostate. Our objective was to identify a mRNA profile in microdissected PIN by microarray analysis and to compare mRNA expression patterns between hyperplastic prostate epithelia, PIN and tumorous epithelia in order to obtain biomarkers for PIN and prostate carcinoma and get insight into the carcinogenesis and development of prostate cancer.

Gene expression profiles were generated from 16 human prostate frozen tissue specimens including 5 hyperplasia, 6 PIN and 5 cancer using Affymetrix[®] Human Genome U133 A (HG-U133A) microarrays. To obtain precise expression profiles for epithelia and avoid contamination of different types of cells and surrounding stoma cells, laser controlled microdissection (LCM) was performed to procure pure epithelial cell populations from cancer, PIN and benign hyperplasia.

Strikingly, clear differences of gene expression patterns were observed among the three groups investigated. A unique mRNA profile was observed in microdissected PIN cells compared to hyperplasia and carcinoma; such as over-expression of cell proliferation related genes CDK11 and AMD1, transcription regulation related gene CRSP2 and enzymes TGM4, CYP1B1 and DPP4 and down-regulation of cell adhesion molecules ZYN, PCDHB3 and tumor suppressor genes CDKN2. Many genes were found gradually modulated in the transition of hyperplasia to PIN to prostate cancer. Several of these genes which were reported up- and/or down-regulated in prostate cancer by other groups were found progressively altered in the transition of hyperplasia to PIN to cancer in this study, such as up-regulation of PSMA, AMACR, FASN and down-regulation of TP63, CDH3 and LAMB3. GSEA identified gene-biochemical pathways significantly changed between different lesions of prostate investigated. The sterol biosynthesis pathway was found increased from hyperplasia to PIN and decreased from PIN to cancer which may imply a possible mechanism of transition from androgen-dependency to androgen-independency of prostate cancer. Autoimmune and inflammatory response-related genes were found down-regulated in prostate cancer compared to hyperplasia and PIN but no down-regulation was found in PIN compared to hyperplasia. This may indicate that a possible immune reaction is triggered to fight against tumor cells upon arrival of an invasive “threshold” and that cancer cells try to counteract these effect, which is not the case for PIN because basal cells are still preserved. Up-regulation of the oxidative phosphorylation pathway was observed in PIN compared to hyperplasia and further increased in carcinoma compared to PIN. We suggest that up-regulation of genes in this pathway may play an important role for metabolic needs of cells in the neoplastic evolution.

We conclude that gene expression profiling separates PIN from benign prostate hyperplasia and prostate cancer; the complex differences in gene expression profiles of the three differentiation states in this study do not allow, a priori, to assume a gradual transition from PIN to carcinoma.