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Implications of plakophilin 1 on gene expression in prostate cancer

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Plakophilins (PKP1-3) are desmosomal plaque proteins belonging to the armadillo (arm)-repeat protein family. PKPs localize not only in cell-cell junctions but also in the nucleus and the cytoplasm. This diverse localization of PKPs implies multiple cellular activities within the cell. PKP3 is associated with the RNA-binding proteins ras-GAP-SH3-binding protein (G3BP), fragile-X-related protein 1 (FXR1), poly (A) binding protein, cytoplasmic 1 (PABPC1) and up-frameshift factor 1 (UPF1) indicating a role in RNA metabolism and post-transcriptional control of gene expression. Both PKP1 and PKP3 play a fundamental role in the development of prostate cancer. The function of the PKP-associated RNA-binding proteins in prostate cancer has not been elucidated until recently. In this thesis, we showed that PKP1 also bound to the RNA-binding proteins. The occurrence of PKP1/3 associated RNA-binding proteins and PKP1/3 was investigated in prostatic cell lines, non-neoplastic prostate and 136 prostatic adenocarcinomas by immunofluorescence and immunoblots. All four RNA-binding proteins G3BP, FXR1, UPF1 and PABPC1 showed a cytoplasmic localization, with the exception of UPF1 that revealed additional nuclear localization. PKP1 and FXR1 were dramatically reduced in tumors with Gleason score >7 and diminished expression of PKP1 and FXR1 appeared to be associated with a metastatic phenotype. In addition, the predominant nuclear accumulation of UPF1 in non-neoplastic glandular cells and low grade tumors switched to a more cytoplasmic phenotype in adenocarcinomas with Gleason score >7.

In order to identify genes that are regulated by PKP1 and to investigate their contributions to prostate cancer, we used a benign prostatic cell line with PKP1 loss of function. By comparing the gene expression profile between the benign prostatic cell line with PKP1 knockdown and control cells, we identified 49 upregulated genes and 50 downregulated genes. We selected candidate genes from distinct functional groups, verified their alteration via quantitative PCRs as well as immunoblots, and compared their expression with a cancer genomic database. Furthermore, by immunofluorescence and immunohistochemistry we explored the expression of the PKP1-regulated gene SPOCK1 in non-neoplastic prostate and 136 prostatic adenocarcinomas and investigated its association with PKP1. SPOCK1 showed a cytoplasmic localization in the glandular epithelium of the prostate and revealed a significant overexpression in prostate cancer.

In summary, PKP1/3 associated RNA-binding proteins and PKP1-regulated genes appear to play a prominent role in prostate cancer progression and metastasis. This further highlights the significance of the non-junctional form of PKP1 in tumor progression of prostate cancer.