Endothelin-1 induced microRNA 15a, inversely correlated to PKC α, is a potential marker to differentiate between benign versus malignant renal tumors in biopsies and in urine samples

Melanie von Brandenstein[1], Jency J Pandarakalam[1], J Herden[2], Gabriele Braun[2], Katharina Wendland[1], H.-P. Dienes[1], Udo Engelmann[2], Jochen W. U. Fries[1]. [1]University of Cologne, Pathology, 50924, Germany, [2]University of Cologne, Urology, 50931, Germany.

NF-κB signaling is a potential therapeutic target in malignant tumors. We have recently shown in malignant renal proximal tumor cells (Caki-1) that after ET-1 stimulation a transcription complex (TC), consisting of NF-κB p65 and MAPK p38 full length, is joined by PKC α. The newly formed TC transmigrates into the nucleus. There, PKC α suppresses the nuclear release of pri-miRNA 15a. Induced by endothelin-1, dropping PKC α levels lead to increased miRNA15a. The identical system can be identified in renal carcinoma, where after nuclear transmigration, PKC α binds directly to pri-miRNA15a in the nucleus. However, the pattern of PKC isoforms differs between malignant RCC versus benign oncocytoma. PKC α – also a component of the TC in tumors - is upregulated in benign oncocytoma, but downregulated in renal cell carcinoma (RCC). Conversely, microRNA15a is upregulated in the nuclei of RCCs and downregulated in oncocytoma. Similar behavior is observed in chromophobe carcinoma, while differences are less pronounced.in papillary RCC Target gene expression (ET-1, ET-A and B-receptor, VCAM-1, IL-6, fractalkine) is particularly high in malignant RCCs. Upregulated miRNA15a can be measured in urine from RCC patients, but is nearly undetectable in other tumors and urinary tract inflammation. Thus, upregulation of miRNA15a may be an important marker to identify malignant clear cell RCC in biopsies and in urine samples.