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# ENDOTHELIN-1 SIGNALING IN DISEASES DAMAGING THE RENAL PROXIMAL TUBULE: PROTEINURIC KIDNEY DISEASE—RENAL CARCINOMA—TUBULOTOXICITY — DIAGNOSTIC APPROACHES AND THERAPEUTIC CONSIDERATIONS

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**T**his presentation highlights results from author's laboratory in the role of endothelin-1 (ET-1) signaling in damaging renal proximal tubules in proteinuric kidney disease, renal carcinoma and tubulotoxicity, involving miRNAs. MicroRNAs (miRNAs) are short non-coding RNAs that can play important roles in cell function and development by targeting mRNA sequences of protein-coding transcripts, resulting in either mRNA cleavage or repression of productive translation. Inflammation/Tumor: Author's research groups has demonstrated that ET-1 plays a major role as a mediator of cellular signaling in primary renal proximal tubule cells, which express both its receptor subtypes (A,B). In proteinuric diseases such as membranous nephropathy or focal segmental sclerosis leading to inflammation and subsequent fibrosis as well as in tubular carcinoma cells (CAKI-1), ET-1 is able to activate a cytoplasmic transcription complex consisting of NF- $\kappa$ B p65, MAPK p38 $\alpha$ , and PKC $\alpha$ . Consequently, PKC $\alpha$  is no longer able to translocate in the nucleus, which leads to loss of suppression of a pri-miRNA15a, maturation of this miRNA in the cytoplasm, its tubular secretion and detectability in the urine. This mechanism seems to exist in minimal change disease, membranous nephropathy and focal segmental sclerosis. Upregulating PKC $\alpha$  levels *in vitro* and in an Adriamycin model of proteinuria results in undetectable levels of miRNA15a in the urine. This may lend itself as marker controlling the effect of therapy and compliance. In renal tumors, high miRNA15a levels (and respective low PKC $\alpha$  levels) are characteristic for malignant clear cell carcinoma being inversely correlated in benign oncocyoma. Tumor resection results in background urinary miRNA15a levels. Meanwhile, the NF- $\kappa$ B p65 has unrestricted nuclear access, transcribing NF- $\kappa$ B responsive genes. Proliferation/Tumor suppression: miRNA15a induces a splice-form of MAPK p38 $\alpha$ , called Mxi-2. We showed that Mxi-2 is a transcription factor in proximal tumor cells. Building a complex with ETS-1 and ERK, it activates p16/p21. Furthermore, in a RISC (RNA-induced

silencing complex) in the cytoplasm together with Ago2 and miRNA1285 it blocks nuclear transmigration of p53, indicating a potential block of tumor suppression. Tubulotoxicity: Through evolution, the regulatory induction of the multiple drug resistant protein 2 (MRP2) via ET-1 receptor B (ETBR) is known. We showed that in an Adriamycin model as well as in human biopsies of proteinuric disease, MRP2 is downregulated. This regulation occurs via ET-1 stimulation of ETBR and activation of miRNA133a, interacting with the 3'UTR region of the MRP2 gene. The excretion of this miRNA could be used as surrogate marker for MRP2 downregulation. This mechanism is also explains tubulotoxicity in renal transplant patients treated with cyclosporine A (CyA): MRP2 responsible for tubular excretion is downregulated in CyA tubulotoxic damage as shown by quantitative immune histology of MRP2 vs. controls (CyA-arteriopathy, CyA non-affected transplants, and normal kidneys). miRNAs could be useful as (i) biomarkers in the urine for renal carcinoma; (ii) indicators of activated signaling pathways in proteinuric disease; (iii) as surrogate marker for potential tubulotoxicity, particularly when tubulotoxic drugs like CyA are considered as treatment in proteinuric diseases such as pediatric FSGS.

## Biography

Prof. Dr. Jochen Fries is the head of a translational pathology laboratory, University Hospital of Cologne, Germany, focusing on the role of endothelin-1, its signal transduction and the function of its newly defined target genes in renal and urogenital pathology. He has published more than 60 research paper in various international journals in the field of Chronic Renal Disease, Cardiac Disease / Vascular Disease, Molecular Therapy / Transplantation Technology/ Stem Cell Technology. He was trained in Surgical Pathology at the Brigham and Women's Hospital and obtained postdoctoral training from the Brigham and Women's Hospital, Children's Hospital, and Harvard School of Public Health in Boston.

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