Netrin-1 deficiency limits cystogenesis in autosomal dominant polycystic kidney disease

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Introduction: We have recently identified a novel mechanism that is involved in the development of ADPKD cystogenesis independent of PKD1 or PKD2 mutation. We have shown that a kidney-specific *Netrin-1* (*NTN1*) transgenic expression (*NTN1-Tg6*) alone is sufficient to develop spontaneous cystogenesis. Kidney-specific *NTN1* transgenic expression induces numerous small cysts as early as in four-week-old mice, and the disease was accelerated along with age. However, the expression of PKD1 and PKD2 was not affected in *NTN1-Tg6* mice raising the possibility that ***NTN1 could be the downstream target of PKD1 or PKD2. Therefore, high NTN1 expression could be an independent prognostic factor for ADPKD***. NTN1 is a laminin-related secreted protein, that plays an important role in axonal outgrowth, cell migration, angiogenesis, and cell survival. *NTN1 mediates its biological functions by interacting with its receptors DCC and UNC5H1-4*. Therefore, the **central hypothesis** of our work is that NTN1 could be recognized as a novel and hitherto unexplored biomarker for ADPKD growth, monitor treatment response, and a novel target for ADPKD drug discovery.

Methods: We used serum, urine, and tissue samples from control and human ADPKD patients. We used kidney-specific *Ntn1* knockout (*Ntn1*$^{F/F}$*-Ksp-Cre*) mice, and orthologous ADPKD mouse models (*Pdk1*$^{F/F}$*-Ksp-Cre*, and *Pkd1*$^{RC/RC}$). We also used a humanized NTN1 mouse monoclonal antibody (NTN1-H-mAb), which specifically blocks the interaction between NTN1 and UNC5H2.

Results: We found an increased expression of NTN1 in human ADPKD tissue, serum, and urine samples. *Ntn1* deficiency limits cystogenesis in the orthologous mouse models. The humanized NTN1 monoclonal antibody efficiently blocks cytogenesis.

Conclusions: Our findings provide a strong rationale that NTN1 levels can be used as a novel biomarker to monitor disease growth and treatment response. Humanized NTN1 monoclonal antibody or a pharmacological inhibitor of NTN1 can be used for the prevention and treatment of ADPKD.

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