Cleavage of Pkhd1 results in a small fragment that localizes and functions within mitochondria.

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Human Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a severe disease caused by mutations in *Pkhd1*, that features rapid renal cyst development *in utero*. However, complete knockout of *Pkhd1* in mouse does not cause a strong cystic phenotype. We propose that in the mouse, *Pkhd1* deletion is a subtle defect which primes the kidney towards cystogenesis. Upon challenge such as disruption of *Pkd1* cleavage, the lack of *Pkhd1* causes enhancement of the cystogenic phenotype.

We show, by combination with an uncleavable *Pkd1* allele, that *Pkhd1* deletion causes rapid cyst development in the mouse kidney. We investigated the C-terminus of *Pkhd1* localization and make-up by western blot, immunofluorescence and *in silico* methods. We used mass spec to evaluate differences between the mitochondrial proteome of Wt and *Pkhd1* deleted kidneys.

We found a mitochondrial localization signal in the C-terminus of *Pkhd1* which is able to direct the C-terminus to mitochondria. We found that disruption of this sequence affects mitochondrial localization of the C-terminus. Cellular fractionation also confirmed that *Pkhd1* C-terminus is able to localize within mitochondria. Deletion of the C-terminal tail of *Pkhd1* is sufficient to enhance cyst development in the *Pkd1* uncleavable model.

We have shown that the C-terminus of *Pkhd1* is cleaved, and transported into mitochondria due to a mitochondria localizing signal within the C-terminal sequence. Deletion of this portion of *Pkhd1* in the uncleavable *Pkd1* background is sufficient to cause cyst development, indicating that the mitochondrial role of the C-terminus of *Pkhd1* is important for maintaining the stability of the renal tubules.

This work was funded by a NIH/NIDDK 1R01 (DK111611) award to Dr Feng Qian entitled:

“The Molecular Mechanisms of Polycystin-1 Proteolytic Cleavage in Kidney Health and Polycystic Kidney Disease”

And a PKD foundation grant (# 215F19a) awarded to Dr Rebecca Walker entitled:
“Relieving the Stress of PKD: A new role of PKHD1 in detoxification mediated via differential cleavage of the intracellular domain”