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.

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