Nature Reviews Nephrology | Published online 25 Jul 2016; doi:10.1038/nrneph.2016.120

CILIOPATHIES

Inpp5e links lipids, cysts and cilia

Mutations in INPP5E cause Joubert syndrome, a ciliopathy that affects various organs and causes renal cysts; however, the mechanisms by which INPP5E dysfunction leads to defective ciliogenesis and cystic kidneys are unclear. In a new study, Ying Cao and colleagues show that Inpp5e modulates ciliogenesis and cystogenesis by regulating basal body docking and cell polarity by controlling the spatial distribution of phosphoinositides (PIs), which are phosphorylated derivatives of phosphatidylinositol (PtdIns). "Previous findings indicated that Inpp5e was required for cilia maintenance but not assembly," explains Cao. "Our work shows that Inpp5e functions in both ciliogenesis and cystogenesis."

In zebrafish, loss of *inpp5e* led to renal cysts, ciliogenesis defects, impaired apical docking of basal bodies and redistribution of apical F-actin towards the lateral membranes of the pronephric epithelium. In addition, the apical localization of PtdIns(4,5)P_2 was lost, whereas PtdIns(3,4,5)P_3 was ectopically localized to the apical membrane.

> "Decreasing PtdIns(3,4,5)P_3 levels ... could provide a new therapeutic avenue to treat Joubert syndrome"

Knockdown or overexpression of Ezrin, which crosslinks PtdIns(4,5)P_2 and F-actin, phenocopied or rescued *inpp5e* knockdown, respectively. Moreover, treatment of *inpp5e* morphants with a PI3K inhibitor reduced the expression and ectopic localization of PtdIns(3,4,5)P_3, restored the apical localization of PtdIns(4,5)P_2, partially rescued ciliogenesis and suppressed cyst formation, and restored kidney function.

"Decreasing PtdIns(3,4,5)P_3 levels with a PI3K inhibitor could provide a new therapeutic avenue to treat Joubert syndrome," says Cao. "In the future, investigating if the spatial distribution of PIs is also affected in polycystic kidney disease would help identify the upstream signals that regulate the spatial distribution of PIs." Future work will also address whether other PtdIns(4,5)P_2-independent signalling pathways, such as AKT, act downstream of PtdIns(3,4,5)P_3 to regulate ciliogenesis.

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ORIGINAL ARTICLE Xu, W. *et al.* The Joubert syndrome protein Inpp5e controls ciliogenesis by regulating phosphoinositides at the apical membrane. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2015080906 (2016)