

PI3K-C2 α regulates Polycystin-2 ciliary entry to prevent kidney cyst formation

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Objective

PI3K-C2 α is a regulator of vesicle recycling at the base of the primary cilium and is required for the targeting of ciliary components. Here we sought to understand whether PI3K-C2 α is required for the targeting of Polycystin-2 to primary cilia and the consequent regulation of kidney cyst formation.

Methods

Homozygous mutation of *Pik3c2a*, the gene encoding for PI3K-C2 α , is embryonic lethal. Hence, the function of PI3K-C2 α in kidney cilia has been studied both *in vitro*, in *Pik3c2a*-silenced IMCD3 cells, and *in vivo*, in *Pik3c2a*-heterozygous mice, using an Ischemia/Reperfusion model of renal injury.

Results

PI3K-C2 α resides at the recycling endosome compartment surrounding the primary cilium base where it controls the activation of Rab8, a key mediator of cargo protein targeting to the primary cilium. Consistently, partial reduction of PI3K-C2 α is sufficient to impair elongation of the cilium both in *Pik3c2a*-silenced IMCD3 cells and in kidney tubules of *Pik3c2a*^{+/-} mice. Importantly, absence of PI3K-C2 α impairs the Rab8-dependent transport of Polycystin-2 to cilia and produces an overactivation of proliferative pathways regulated by ciliary Polycystins, such as the mTOR and MAPK pathways. Both defects can be rescued by transfection of constitutively active Rab8. In line with defective Polycystin signaling, heterozygous deletion of PI3K-C2 α in mice causes an overall deregulation of proliferative signals in response to Ischemia/Reperfusion-

induced renal damage, and this condition predisposes to cyst development.

Conclusion

These results indicate that PI3K-C2 α is required for the transport of ciliary components like Polycystin-2 and that reduction in PI3K-C2 α levels is sufficient to enhance susceptibility to cystic kidney disease.

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