PC2 degradation is altered in Pkd1-null cells

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INTRODUCTION ADPKD is a hereditary disorder that affects 1:1000 to 1:500 people and is characterized by fluid-filled cysts that arise from renal tubules. ADPKD results from mutations in either the PKD1 or PKD2 gene, which encode the gene products polycystin 1 (PC1) and polycystin 2 (PC2), respectively. Although PC1 and PC2 have been studied intensively, information on how they function is still emerging. It has been previously shown that PC2 is degraded via proteasome in MDCK cells. We have shown that overexpression of PC1 accelerates PC2 degradation via the autophagy in MDCK cells. It is not clear whether knockout of Pkd1 has an effect on PC2 degradation. Here we have investigated PC2 degradation in *Pkd1*-null cells.

METHODS We have treated *Pkd1*-null and control cells with cycloheximide to block translation and then inhibited autophagy with bafilomycin and proteasome with MG132, and examined PC2 expression. Next, we inhibited HDAC6 activity and examined PC2 expression.

RESULTS Inhibition of proteasome with MG132 prevented degradation of PC2 in control cells, suggesting that PC2 is degraded via proteasome when PC1 is expressed. Inhibition of autophagy with bafilomycin prevented degradation of PC2 in *Pkd1*-null cells, suggesting that PC2 is degraded via autophagy when PC1 is absent. PC2 immunoprecipitation had higher affinity for p97/VCP, a proteasome substrate, in control cells than in *Pkd1*-null cells, indicating that PC2 is degraded via proteasome when PC1 is expressed. Chemical inhibition of HDAC6 increased degradation of PC2 in both *Pkd1*-null and control cells suggesting that HDAC6 plays a key role in PC2 expression.

CONCLUSION PC2 is mainly degraded via proteasome when PC1 is expressed and via autophagy when PC1 is absent. HDAC6 plays a key role in PC2 expression/degradation in both *Pkd1*-null and control cells. Further studies will have to determine whether defective degradation of PC2 in *Pkd1*-null cells leads to defective trafficking.