Notch3 is important in maintaining the cellular integrity of vasculature and collecting ducts in polycystic kidney disease

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Introduction: We have previously reported that Notch3 is activated in renal cyst lining cells of PKD patients and mouse models of PKD. Inhibition of Notch pathway reduced cystogenesis in microcysts from human ADPKD cells grown in 3D collagen gels. Here we determined the *in vivo* effects of Notch inhibition on PKD progression.

Methods: Fast progressing mouse models of PKD (*cpk* and *Pkd1$^{f/f}$: pkhd1,cre*) and slow progressing model of PKD (*Pkd1$^{RC/RC}$*) were injected with Notch inhibitor (GSIXX, 500μg/100g body weight). *Pkd1$^{f/f}$: pkhd1, cre* mice and *cpk* mice were injected starting postnatal day 10. The injections for *Pkd1$^{RC/RC}$* mice were started at 4 months of age for 10 consecutive days. Further, Notch3 was also genetically deleted in *cpk* mice and effects were studied on vasculature and collecting duct cells.

Results: A single dose of GSIXX was lethal for both *cpk* and *Pkd1$^{f/f}$: pkhd1 cre* mice. These mice died after one day of injections while the wildtype littermates did not show any effects. *Pkd1$^{RC/RC}$* mice survived the GSIXX treatments however, showed increased kidney to body weight and increased cystic index. Genetic ablation of Notch3 also proved lethal in *cpk* mice. We found that Notch3 is important to sustain normal vasculature, specifically in PKD. Further, we show that Notch3 inhibition dysregulated cilia composition in the collecting duct compartments in PKD mice and was related to dysregulation of principal cells and intercalated cell ratio.

Conclusions: Notch signaling, specifically Notch3 is important to retain the function of collecting duct and vasculature in PKD.

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