Cystic Epithelial Vasopressin Type-2 Receptor Signaling Regulates Interstitial Fibrosis in Polycystic Kidney Disease

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BACKGROUND

Progressive tubulo-interstitial fibrosis, which involves excessive extracellular matrix (ECM) deposition and tissue remodeling is thought to be a major cause for loss of renal function and end stage renal disease in polycystic kidney disease (PKD). However, the mechanism for development of renal fibrosis in PKD is currently unclear. A large population of myofibroblasts, the primary producers of ECM are often found in the peri-cystic area in human and mouse PKD kidneys. We examined the hypothesis that cystic epithelial cells can modify the cystic microenvironment to favor fibrosis by activating myofibroblasts.

METHODS

To determine if cystic epithelium regulates fibrosis, renal tubular epithelium- specific vasopressin type-2 receptors (V2R) were stimulated or inhibited in pre-weaning and adult inducible tubule specific Pkd1 gene knockout mice with cystic kidneys. Wild type and PKD mice were treated with the V2R agonist dDAVP, or the antagonist OPC31260 by daily intraperitoneal injections for 3 days.

RESULTS

Treatment with dDAVP increased ECM deposition and myofibroblasts in PKD mouse kidneys, while OPC31260 treatment had the reverse effect. Expression of connective tissue growth factor (CTGF), a matricellular protein and yes associated protein (YAP) a transcriptional regulator of CTGF were also increased in the dDAVP treated PKD mouse kidneys. Moreover, CTGF and YAP were found to be expressed in mouse and human ADPKD renal cystic epithelium, and CTGF secreted by cultured human ADPKD epithelial cells induced myofibroblast activation and migration *in vitro*. Furthermore, YAP inactivation suppressed CTGF production and cyst expansion *in vitro*, and fibrosis in Pkd1 gene knock out mice.

CONCLUSIONS

These results suggest that epithelial specific V2R stimulation can stimulate YAP dependent CTGF production to activate interstitial myofibroblasts and renal fibrosis in PKD.