Lack of α-intercalated cells to secrete NGAL as the cellular and molecular basis of urinary tract infection in autosomal dominant polycystic kidney disease.

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INTRODUCTION

Urinary tract infection (UTI) is a common feature of autosomal dominant polycystic kidney disease (ADPKD) with ~30–50% of ADPKD patients having at least one UTI during their lifetime. However, the underlying cellular and molecular mechanisms linking ADPKD to UTI remain unaddressed.

METHODS

We generated *Pkd2*$^{f/f}$ *Aqp2Cre* mice to disrupt *Pkd2* in Aqp2^{+} progenitor cells, which give rise to all known cell types of the connecting tubule/collecting duct (CNT/CD). Immunofluorescence (IF) staining for various segment- and/or cell-specific markers was conducted. Over 1000 CNT/CD cells from 3 *Pkd2*$^{f/f}$ *Aqp2Cre* and 3 WT mice for each IF combination were categorized and counted based on the marker expression. Aqp2, V-ATPase B1B2 and AE1 were used as markers for principal cells (PC), intercalated cells (IC) and α-IC, respectively. Kidneys from ADPKD patients (n=27) and minimal change disease patients (MCD) as normal control (n=5) were analyzed similarly.

RESULTS

Pkd2$^{f/f}$ *Aqp2Cre* mice developed severe PKD, died by P17, had a reduced IC/PC ratio from 37.61±1.23% in WT to 7.45±1.08%, and completely lost α-IC at P17. Neutralized urine from *Pkd2*$^{f/f}$ *Aqp2Cre* mice is significantly less inhibitory for bacterial growth than that from WT mice. In P6 *Pkd2*$^{f/f}$ *Aqp2Cre* mice, cysts began to be detectable with occasional presence of α-IC. TUNEL assay showed that IC, particular α-IC, were more apoptotic than PC. While all PC and IC markers were readily detectable in each of MCD samples, cysts containing AQP2^{+} cells were found only in 13 ADPKD samples. Among these 13 ADPKD samples, we counted >4000 CNT/CD cells and found that ADPKD diminished the IC/PC ratio from 26.07±6.19% in MCD to 10.12±6.53%. None of the ADPKD kidneys had AE1^{+} cells in Aqp2^{+} labeled cystic structure. Seldom AE1^{+} cells were observed in apparently normal CNT/CD of some ADPKD kidneys.

CONCLUSION

Pkd2 deletion in Aqp2^{+} progenitor cells is sufficient for PKD development, and α-IC are selectively depleted with the disease development in both mice and human. The lack of α-IC to acidify urine and secret neutrophil gelatinase-associated lipocalin (NGAL) that chelates siderophore-containing iron may link ADPKD to UTI.