Chronic kidney injury induced by repeated low-dose cisplatin treatment accelerates cyst progression in a mouse model of ADPKD

Zhang Li, PhD; Sreelakshmi Cherakara, MS; Raksha P. Hombal, BS; Courtney J. Haycraft, PhD; Reagan S. Andersen, BS; Bradly K. Yoder, PhD
Cell, Developmental and Integrative Biology; University of Alabama at Birmingham, Birmingham, AL, USA

Introduction: Polycystic kidney disease (PKD) is one of the most common genetic renal diseases, characterized by formation of large fluid-filled cysts. Links between cyst progression and renal injury have been reported in multiple PKD animal models. However, most studies focus on acute injury such as ischemia/reperfusion. Here we examined the response of kidney to chronic injury, and evaluated how the loss of PKD2 altered the injury response that accelerates cystogenesis in PKD.

Methods: A repeated low-dose cisplatin treatment (5mg/kg BW; IP injection 1x/week for 4 weeks) was utilized to induce chronic renal injury in WT and Pkd2 mutant mice. To evaluate the effects of injury on cyst formation, we analyzed renal injury, fibrosis, and cystic index from kidneys harvested at Day3, Day7 and 5weeks after the last cisplatin treatment.

Results: Comparing kidneys from WT and Pkd2 mutant mice both treated with cisplatin, there were more injured cells at Day3, but less injured cells at Day7 post cisplatin treatment, as shown with Sox9 or Kim1 expression by immunofluorescence staining. Also, more apoptotic cells, as indicated by cleaved caspase 3 staining were observed in Pkd2 mutant kidneys at Day7 post cisplatin treatment. Interestingly, in contrast to WT kidneys presenting increased fibrosis after cisplatin treatment, Pkd2 mutant kidneys showed an increased dilation in proximal tubules, and accelerated rate of cyst progression comparing to non-treated mutants at Day7 and 5weeks post cisplatin, respectively.

Conclusions: These data indicate chronic kidney injury can also promote cyst progression in Pkd2 mutant mouse models. Additionally, it suggests that PKD2 proteins function in regulating repair processes following chronic injury, and defects of which will render the cells more susceptible to injury. This will result in more cell death and tubule dilation, eventually triggering rapid cyst progression.

Funding Sources: PKD Foundation Fellowship 959949 (ZL); NIH R01 DK115752 (BKY).