Failed repair in renal injury response correlates to cyst formation in adult *Pkd2* mutants

Sreelakshmi Cherakara, M.S; Zhang Li, Ph.D.; Courtney J. Haycraft, Ph.D. and Bradley K. Yoder, Ph.D.
Department of Cell, Developmental, and Integrative Biology
University of Alabama at Birmingham, Birmingham, Alabama, US

Introduction: Autosomal Dominant Polycystic Kidney Disease is caused by PKD1 or PKD2 gene mutations, resulting in progressive renal cyst formation. Previous murine studies of conditionally mutated *Pkd2* from our lab have shown slow progressive cyst formation that is accelerated upon renal injury, which suggests that PKD2 has a regulatory role in injury response that, when disrupted, drives cyst formation.
Methods: Renal injury was induced by IP injection of cisplatin (9.0mg/kg BW) in adult-induced CAGG-CreERT2*; Pkd2* mutant mice. We tracked the expression of a known renal injury marker, SOX9, to assess the renal injury at 3-, 7-, 14-, 28-, and 35 days post-cisplatin using a fluorescence microscope image. The kidney phenotype was characterized using changes in tubule dilation and fibrosis.
Results: The number of cells expressing SOX9 peaked at 3- and 7-days post-injury in both *Pkd2* mutants and controls, respectively, and decreased through 28 days post-injury. On day 28, *Pkd2* mutants showed an increased number of persistent SOX9-expressing cells, indicative of failed repair, compared to controls. An increase in SOX9+ cells was observed from D28 to D35 post-injury in *Pkd2* mutants, while no change was seen in controls. The baseline tubule dilation and fibrosis were higher in the injured mutants compared with the controls.
Conclusions: These data show that *Pkd2* mutants respond to cisplatin-induced injury through upregulation of SOX9, increased tubule dilation, and fibrosis. The increase in the number of failed repair cells in *Pkd2* mutants compared to controls at D28 shows a defect in repair processes, suggesting that PKD2 may be involved in the repair response pathway. The increase in SOX9+ cells from D28 to D35 may indicate that the malrepaired cells are proliferating or that additional cells are being further injured in *Pkd2* mutants.
Funding: NIH/NIDDK R01DK115752, R01DK122939 (BKY)