Role of Interferon-gamma in Cyst Formation After Acute Kidney Injury

Morgan E. Smith, B.S.[1]; Ummey Khalecha Bintha Ahmed, Ph.D.[1]; Katharina Hopp, Ph.D. [2]; Kurt A. Zimmerman, Ph.D.[1.]
[1]Division of Nephrology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, U.S.A.
[2]Department of Medicine, Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, Colorado, U.S.A.

Introduction: Acute kidney injury (AKI) is known to accelerate cystogenesis in conditional ciliopathy (*Ift88*) mice. Our lab previously showed that genetic deletion of adaptive immune cells significantly reduced cystic disease in *Ift88* mice after AKI. Additionally, using single-cell RNA sequencing, we found that T cells isolated from conditional *Ift88* mice after AKI had enriched expression of the cytokine interferon-gamma (IFN-γ). Based on these data, we hypothesize that T-cell-derived IFN-γ is a significant contributor to the accelerated cystogenesis that is seen following AKI in ciliopathy mice.

Methods: To test this hypothesis, we crossed conditional *Ift88* mice to mice lacking IFN-γ. At 8 weeks of age, we induced loss of *Ift88* and primary cilia through tamoxifen injection followed by administration of folic acid to induce AKI at 11-12 weeks of age; sodium bicarbonate solution was used as a vehicle-only control. Kidneys were harvested 56 days post-injury and cystic severity was measured by quantifying cystic index. We also analyzed changes in immune cell populations at the same time point using flow cytometry.

Results: Analyses of cyst severity 56 days post AKI indicate that conditional *Ift88* IFN-γ knockout mice had a significant reduction in the severity and number of renal cysts compared to conditional *Ift88* IFN-γ control mice. Analysis of flow cytometry data indicates a correlative reduction in the number of kidney resident macrophages and neutrophils in the conditional *Ift88* IFN-γ knockout AKI mice compared to conditional *Ift88* IFN-γ control AKI mice.

Conclusions: Collectively, our data indicate that T-cell-derived IFN-γ is a major contributor to accelerated cystic disease that is observed in conditional *Ift88* mice post AKI. Ongoing studies are addressing the specific T cell subset involved in injury-accelerated disease and the potential mechanism through which IFN-γ accelerates cystic disease in conditional *Ift88* mice following AKI.

Funding sources: Polycystic Kidney Disease Research Foundation grant 826369, Presbyterian Health Foundation (PHF) Team Science grant 952396, National Institutes of Health (NIH) N5K01DK119375-04