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 (Ifit88) mice. Our lab previously showed that genetic deletion of adaptive immune cells significantly reduced cystic disease in Ifit88 mice after AKI. Additionally, using single-cell RNA sequencing, we found that T cells isolated from conditional Ifit88 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 Ifit88 mice to mice lacking IFN-γ. At 8 weeks of age, we induced loss of Ifit88 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 Ifit88 IFN-γ knockout mice had a significant reduction in the severity and number of renal cysts compared to conditional Ifit88 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 Ifit88 IFN-γ knockout AKI mice compared to conditional Ifit88 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 Ifit88 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 Ifit88 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