Seed Grant - Esther Speer (PI), Sandeep Mallipattu (Co-PI)

Novel therapeutic approach in a murine model of neonatal sepsis-induced acute kidney injury

Overview/Abstract

The overall goal of this project is to better understand the sepsis-induced acute immunological, mitochondrial, structural and functional alterations and their impact on longitudinal kidney outcome in a newborn mouse bacterial sepsis model. Employing this model, our project further aims to study the potential renal benefits of adjunctive anti-inflammatory treatment in addition to antimicrobial therapy.

According to the WHO, nearly 1 million newborns die annually worldwide during their first four weeks of life due to severe infections including sepsis, which is particularly prevalent among preterm newborns below 37 weeks gestation, who represent over 10% of all births globally. Neonatal sepsis triggers an intense host inflammatory response that contributes to increased morbidity and mortality including acute kidney injury (AKI) in affected term and preterm newborns. High rates of AKI have been reported among preterm newborns during the neonatal period, which places them at risk for subsequent chronic kidney disease, decreased renal function and hypertension. The mechanisms on how neonatal infection and inflammation leads to AKI, and how neonatal AKI promotes subsequent chronic kidney disease, remain however poorly understood, despite its high prevalence and impact on neonatal and long-term health. Several multicenter studies only recently began to investigate the prevalence, risk factors and longitudinal outcomes of neonatal AKI, and no effective treatment interventions are available thus far.

Pentoxifylline (PTX), a non-specific phosphodiesterase inhibitor and methylxanthine derivative with anti-inflammatory, antioxidant and microcirculatory properties, is a candidate adjunctive therapy in addition to antibiotics for newborn sepsis, that showed decreased all-cause mortality without adverse effects in several small clinical trials. Recent reports suggest that PTX may protect against kidney injury during sepsis by improving mitochondrial integrity through the cAMP-CREB pathway, thereby preventing subsequent ongoing inflammation and fibrosis. In adult rodent models, PTX has demonstrated renal protection from ischemia and inflammation. Based on these reports and our own preliminary data on the inhibition of PTX of inflammatory and renal injury biomarkers in a neonatal *Escherichia coli* sepsis model, we hypothesize that murine neonatal sepsis causes mitochondrial damage and increases biomarkers of renal injury and inflammation, which can be mitigated with adjunctive PTX therapy in addition to antibiotics. We further hypothesize that survivors of murine neonatal sepsis demonstrate ongoing inflammation and fibrosis into adulthood with ensuing structural and/or functional changes, that may be mitigated or prevented with adjunctive PTX sepsis therapy during the neonatal period.

The aims of our project are therefore to characterize the immunological, mitochondrial, and structural changes of AKI during murine neonatal sepsis, and the effects of adjunctive PTX on these kidney alterations, through analysis of inflammatory cytokines, chemokines and biomarkers of tissue injury, gene expression of mitochondrial function, renal functional assays, histology and immunohistochemical analysis of renal injury patterns and cellular infiltration. Furthermore, our aim is to investigate the longitudinal structural and functional kidney outcomes in young adult mice that have survived neonatal bacterial sepsis, and the potential role of PTX administered during the neonatal sepsis episode on these outcomes.

We anticipate that these experiments will validate out hypothesis, and find that neonatal sepsis promotes the expression of inflammatory and tissue injury biomarkers and mitochondrial dysfunction, and leads to structural and functional changes in neonatal kidneys that last into young adulthood, and might be mitigated with adjunctive anti-inflammatory therapy during neonatal sepsis. These data are expected to generate several manuscripts on the acute and chronic sepsis-induced renal changes and treatment effects. Based on the findings resulting from this Seed Grant, an R21 application will be submitted to the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.