Objective

- To test the hypothesis that exogenous activation of AMPK with AICAR can limit the septic immune response and yield protection against sepsis-induced AKI.

Methods

Animal experiment: C57BL/6 mice cecal ligation and puncture (CLP)-induced sepsis model (n=60) exposed to AICAR 24h before CLP.

- Endpoints: Primary - Cr, BUN, Cystatin C; secondary – Cytokines, ICAM-1, and vascular leak.

In vitro experiments: Macrophages, bone marrow neutrophils (PMN) and renal endothelial cell culture exposed to Lipopolysaccharide (LPS).

- Endpoints: Cytokine release (macrophages); ICAM-1 expression by endothelial cells; PMN adhesion.

Background

- The pathophysiology of sepsis-induced AKI remains unknown.
- A highly conserved cellular defense mechanism is conservation of energy by re-prioritization of energy utilization.
- AMPK, a master regulator of cellular energy metabolism, is at the forefront of such response.

Results

- Figure 1. AMPK over-activation prevented elevation in Creatinin, BUN and Cystatin C after CLP.
- Figure 2. AMPK over-activation limited the inflammatory response in vivo.
- Figure 3. AMPK over-activation limited the inflammatory response in vitro.
- Figure 4. AMPK over-activation limited the expression of ICAM-1 (red stain) in kidney (A) and renal endothelial cells (B).
- Figure 5. AMPK limited the adhesion of PMN (A) and vascular leak (B).
- Figure 6. AMPK over-activation protected the glomerular microvasculature by decreasing endothelial fenestrations.

Conclusion

- Exogenous AMPK activation by AICAR 24 hours before CLP prevented sepsis-induced AKI, decreased cytokine release, endothelial activation and vascular leak in early sepsis.
- This protection may be due to modulation of the inflammatory response and protection of the microvasculature rather than energy conservation mechanisms.