Kidney tubular AMP-activated protein kinase (AMPK) activation is protective against Sepsis-associated acute kidney injury (S-AKI)

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Introduction

- S-AKI is common and increases mortality.
- Pharmacologic AMPK activation decreases the development of S-AKI and improves survival in rodent models of sepsis.
- Role of kidney AMPK activation in the protection against AKI during sepsis remains unclear.
- Kidney injury protection may be mediated through a ***Tolerance*** mechanisms, defined as the capacity of cells and tissue to limit injury independently of the ability to clear the bacterial burden.

Hypothesis

Activation of AMPK in tubular epithelial cells (TEC) protects against the development of S-AKI through a ***Tolerance*** mechanisms.

Methods

Animals - Rodents

- Conditional kidney tubule-specific AMPK knockout (KO) system on C57BL/6 background: *AMPKα1/α2$^{flox/flox}$/Pax8-rTA/LC1* and wild type littermates (n=6-20/group).

AMPK KO induction

- AMPK KO and WT animals were treated with doxycycline (2mg/ml doxycycline, 5% sucrose in water) for 3 weeks to induce KO of AMPK in TEC.

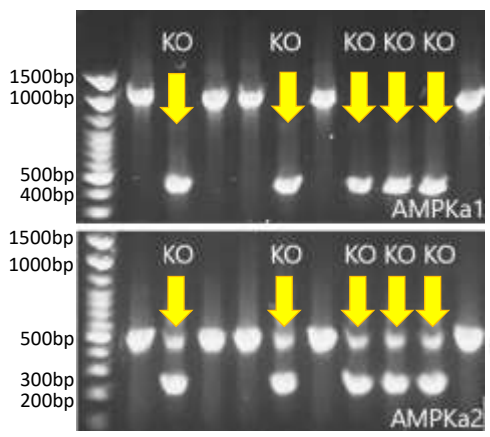


Fig 1A. AMPK α1= Flox 1200bp, KO 500bp; AMPK α2= Flox 500bp, KO 300bp.

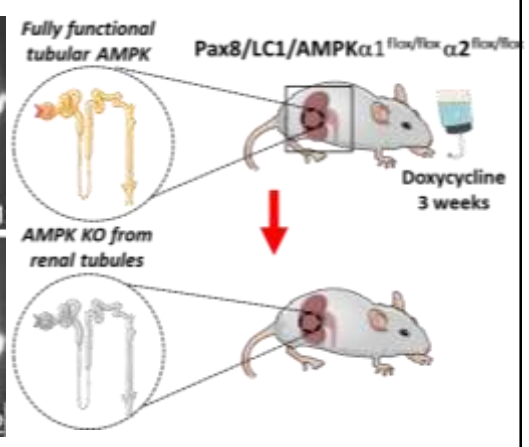


Fig 1B. Kidney AMPK KO model induction with doxycycline-based treatment.

Exposure

- Cecal ligation and puncture (CLP).

Treatment

- AMPK activator, AICAR (500mg/kg/IP) 24h before CLP.

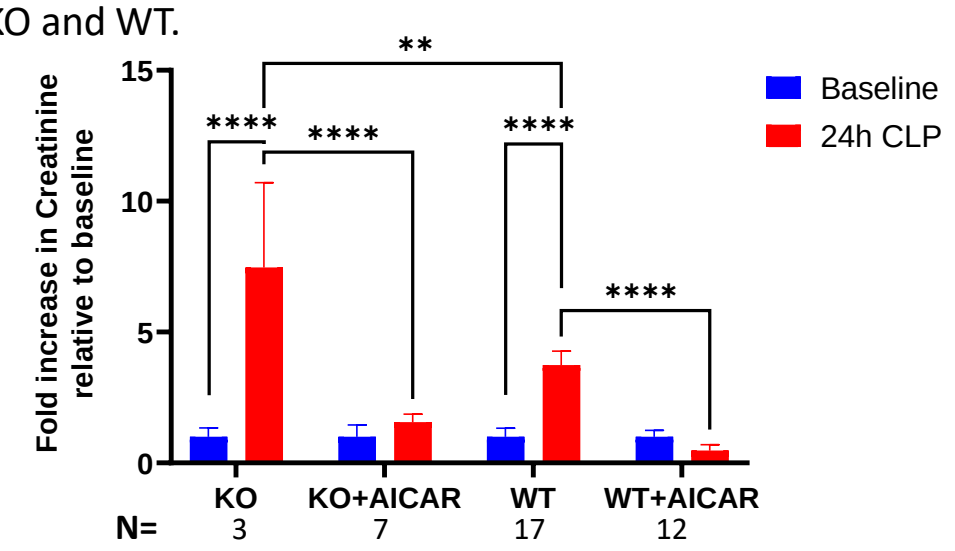
Outcomes at 24h

- **AKI:** Increase in plasma creatinine (Cr) ≥ 50% from baseline to 24h post-CLP.
- **Survival:** At 24h
- **Peritoneal bacterial burden (Tolerance):** Peritoneal bacterial burden measured by quantifying colony-forming units (CFU) in peritoneal lavage fluid (PLF).

Results

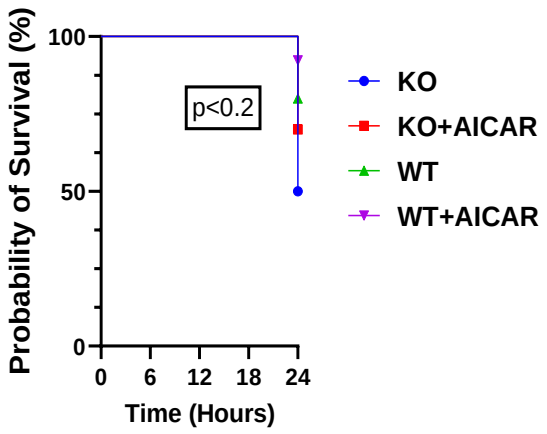
Kidney Injury

- AMPK KO animals had more severe AKI after CLP than WT.
- AMPK activation with AICAR limited the development of AKI in AMPK KO and WT.



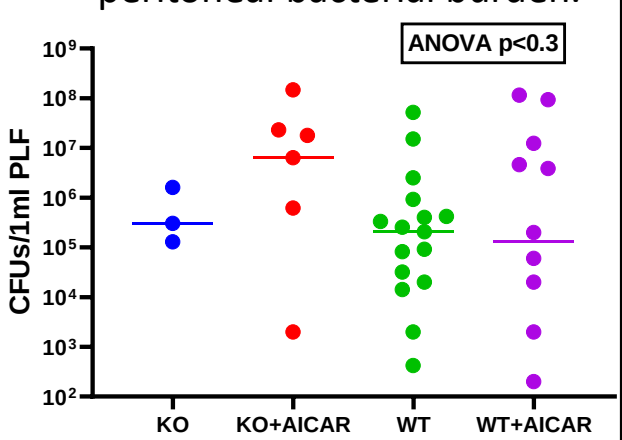
Survival at 24h

- AMPK KO had a trend toward worse survival than WT.



Peritoneal Bacterial Burden

- There were no differences in peritoneal bacterial burden.



Conclusions

- Kidney AMPK expression decreases S-AKI severity and possibly death during sepsis.
- The protective effects of AICAR against S-AKI are independent of kidney AMPK expression.
- AMPK-induced protection is independent of the bacterial burden, suggesting AMPK operates through a tolerance mechanism.

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