Mg53 Mitigates Acute Kidney Injury in a Large Animal Model of Isolated Traumatic Brain Injury

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Introduction

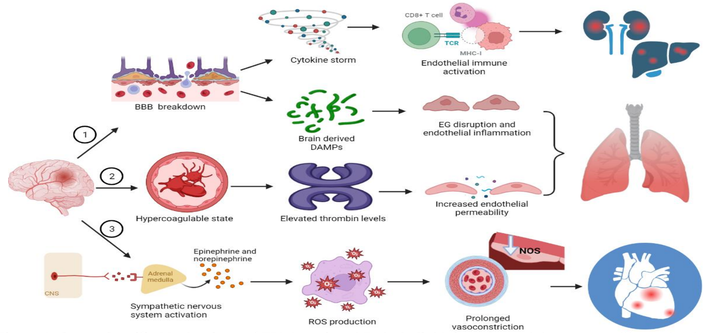


Figure 1: Organ-Specific Mechanisms of TBI-Associated Endothelial Injury: *Potential organ-specific mechanisms of TBI induced endothelial damage. TBI- traumatic brain injury; BBB-Blood brain barrier; DAMPs-damage-associated molecular patterns; ROS-Reactive oxygen species; TCR- T cell receptor; MHC I- major histocompatibility complex I; EG-Endothelial glycocalyx; NOS-Nitric oxide synthase.*

- TBI can trigger a variety of pro-inflammatory and hypercoagulable pathways leading to distant organ dysfunction.
- Clinical data suggest severe AKI + TBI have important morbidity implications (both in transplantation and trauma).
- The mechanisms of TBI induced MOD are unknown and may be related to TBI-associated endothelial injury, hemodynamic changes, and side effects of TBI treatment.
- Realistic large animal models to study this phenomena are lacking.
- Mg53, a cell repair protein, has shown to protect a variety of organs for various insults. We have previously shown improvement in brain lesion size 6-7 hrs after TBI.

Research Objectives

Aim 1: Identify the impact of TBI on kidney injury in a realistic swine model of isolated TBI.
Aim 2: Can treatment with Mg53 attenuate TBI induced acute kidney injury?

Methods

- Yorkshire swine, 40-45kg (n=5/group), anesthetized and instrumented.
- **Injury:**12mm diameter controlled cortical impact.
- **Treatment:** Mg53 (2mg/kg) or Saline Vehicle was given immediately after TBI.
- Plasma and serum collected at baseline, 2h, 4h and 6 h post injury.
- **Statistical Analysis:** all values reported as averages ± SD, unpaired student T-test. used to determine statistical significance (p≤ 0.05) between two groups.

Results

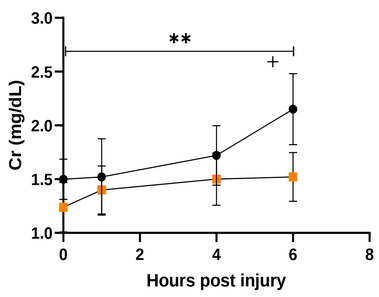
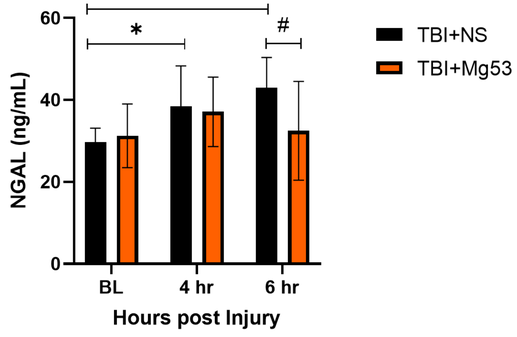


Figure 2: Isolated TBI causes acute elevation in creatinine, which is mitigated by treatment with Mg53. *Isolated TBI results in a significant increase in serum creatinine in as little as 6 hours after injury (**,p=0.0018 between baseline and 6-hour post injury). In animals with TBI treated with mg53, there was no significant increase in creatinine. Creatinine in the TBI alone group was significantly higher at hour 6 compared to animals treated with mg53 (+, p=0.012). Cr= creatinine*

Figure 3: Serum NGAL significantly increases after TBI starting at 4 hours after injury, which is mitigated by Mg53. *Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) was tested using ELISA with pig specific antibody. In the TBI control group, NGAL increased from baseline starting at 4 hours after injury (*,p=0.014) and continued to increase 6 hours (**,p=0.0002). NGAL did not increase significantly from baseline in the TBI+Mg53 group at 4 hours or 6 hours post injury. NGAL was significantly higher at 6 hours post injury in the TBI control compared to TBI+Mg53 group (#, p=0.0419).*



TIMP-1 levels in mouse model of TBI

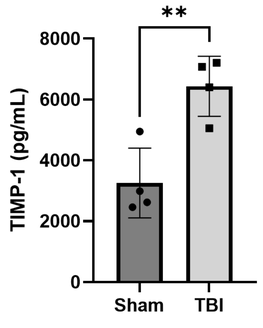


Figure 4: TIMP-1 levels significantly increase in a mouse model of isolated TBI. *Plasma from mice subjected to isolated TBI collected 24 hours post injury were compared to plasma from non-injured mice. Using Luminex immunoassay, levels of TIMP-1, a marker of acute kidney injury, was compared. Animals in the TBI group (n=4) had significantly elevated TIMP-1 compared to controls (n=4) (p=0.0057). WT=wildtype*

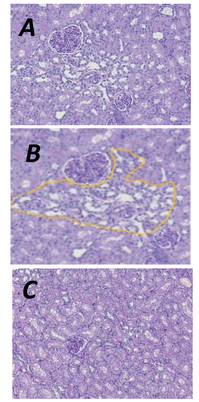


Figure 5: Histologic analysis of swine kidney shows amelioration of TBI-induced proximal tubular epithelial damage with post-TBI treatment of Mg53. *Representative image of Periodic Acid-Schiff (PAS) stained kidney samples of swine euthanized 6 hours following sham control* ***(A)****,isolated TBI* ***(B),*** *or post-TBI treatment with Mg53* ***(C)****. Animals who had undergone isolated TBI were found to have evidence of proximal tubular damage as highlighted in yellow* ***(B)****.*

Summary

- Evidence of acute kidney injury can be observed in two different animal models of isolated TBI.
- Isolated TBI leads to acute kidney injury that is evident as soon as 4-hours post injury.
- Treatment with Mg53 is both neuroprotective and kidney protective, though this protective mechanism remains unknown.

Conclusions

- TBI has important effects on distant organ injury. Understanding the mechanism of TBI-induced organ injury using a clinically relevant large animal model has the potential to influence a variety of clinical scenarios from transplantation medicine to trauma care.
- **Disrupting the Neuro-Endothelial axis could mitigate the impact of TBI induced distant multi-organ damage.**

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