Efficacy of MPLA Preconditioning for Severe Radiation-Combined Burn Injury: Improving Survival and Reducing Vascular Leakage

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BACKGROUND

Radiation-Combined Burn injury (RCB)

- Escalating global instability makes nuclear weapon use or attacks on nuclear power plants a realistic threat.
- In radiological events, up to 70 % of victims may have whole-body irradiation (WBI) plus physical trauma.
- Among these patients, thermal burns are the most common associated trauma, producing **Radiation-Combined Burn injury (RCB).**
- RCB patients often deteriorate catastrophically during the acute phase because of complex, poorly understood **synergistic effects**.
- **Study objective:** Identify new Medical Countermeasures (MCMs) that can rescue severely injured RCB patients during the acute phase.

MPLA preconditioning

- **MPLA** is a detoxified derivative of the lipid A component of **LPS** that retains TLR4 agonist immunity and activates innate immune responses.
- Low-dose endotoxin preconditioning has various known effects on the immune system.
  - **Enhances phagocytic activity**
  - **Limits excessive inflammatory responses**

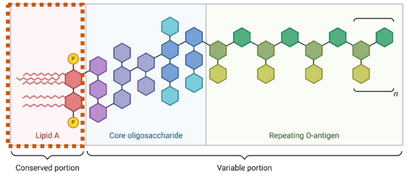


Figure 1. Schematic structure of lipopolysaccharide (LPS), highlighting the lipid A portion

This makes **MPLA preconditioning an attractive medical countermeasure candidate for RCB**.

METHODS

Mouse Model: C57BL/6J, male, 8–12 weeks old, 20–25 g
Whole Body Irradiation (WBI): 6 Gy of X-ray (0.4 Gy/min)
Burn injury (20% TBSA Burn): 20% Total Body Surface Area full-thickness burn + N.S. 500 μL *i.p.*
Radiation-Combined Burn (RCB): 6 Gy WBI → 20% Burn, + N.S. 500 μL *i.p.*

MPLA injected *i.p.* once per day for two days.

- **MPLA + (preconditioning)** : MPLA 10 μg + 500 μL N.S.
- **MPLA – (vehicle)** : 500 μL N.S.

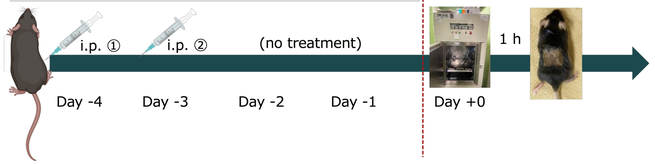
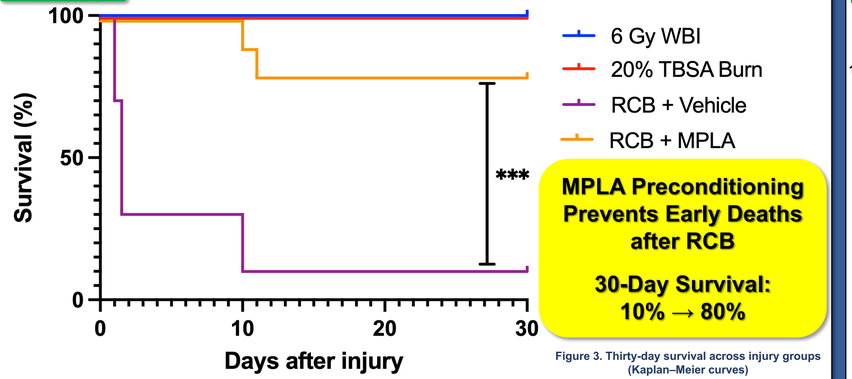


Figure 2. Experimental timeline and injury protocol

- **Survival**
- **Vascular permeability**
- **Intestinal permeability**
- **Cytokine & Chemokine**

etc.

RESULTS

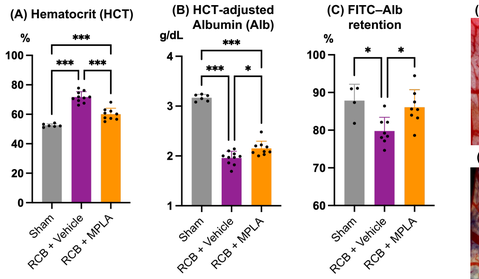


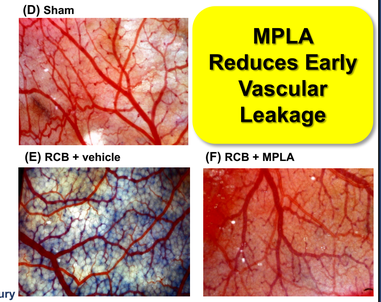
MPLA Preconditioning Prevents Early Deaths after RCB

30-Day Survival: 10% → 80%

Figure 3. Thirty-day survival across injury groups (Kaplan–Meier curves)

-WBI alone (6 Gy) and Burn alone (20 % TBSA): **100% survival**
-RCB + vehicle (purple line): 30-day survival fell to **10%**, most deaths occurring within the **first 24–48 h**.
-RCB + MPLA preconditioning (orange line): boosted 30-day survival to **80%**.
-The benefit is concentrated in the **acute phase**, preventing the early deaths from RCB. (n=10), *** $p < 0.001$ (log-rank)



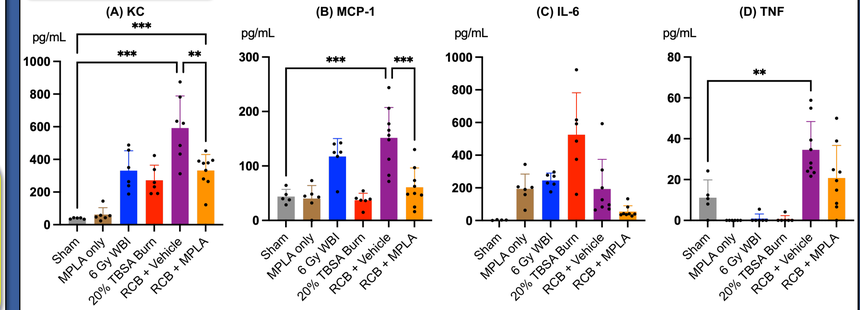


MPLA Reduces Early Vascular Leakage

Figure 4. Findings related to hemoconcentration and vascular leakage at 6 h post-injury

(A) RCB caused marked **hemoconcentration**, which was attenuated by MPLA preconditioning.
(B) MPLA preconditioning preserved **serum albumin** (HCT-adjusted) after RCB.
(C) MPLA preconditioning increased intravascular FITC–**albumin retention** after RCB.
(D–F) Mesenteric Evans blue extravasation was observed using a stereomicroscope; **leakage** was increased after RCB and reduced by MPLA preconditioning.
Together, these findings indicate that **MPLA preconditioning attenuates early vascular leakage after RCB.**
(n = 6–10, mean ± SD), * $p < 0.05$, *** $p < 0.001$

RESULTS (continued)



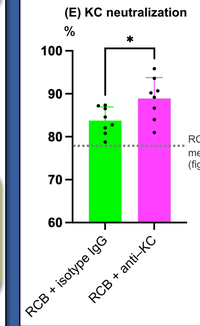


Figure 5. Early Chemokine and Cytokine Responses and Identification of KC as a Key Mediator of Vascular Leakage at 6 h after Injury

KC is a Key Link between Burn–WBI Interaction and Vascular Leakage

Chemokines
(A), (B) KC (Keratinocyte-derived chemokine) and MCP-1 (Monocyte chemoattractant protein-1) increased after RCB and were reduced by MPLA preconditioning.
Cytokines
(C), (D) IL-6 and TNF increased after RCB, with no significant reduction by MPLA at 6 h.

→ **KC showed the most pronounced increase** and is known to increase after **both burn injury and WBI.**

KC neutralization
(E) Anti-KC antibody administered 1 h before RCB significantly increased FITC–albumin retention.
Significance markers are shown only for Sham vs RCB + vehicle and RCB + vehicle vs RCB + MPLA.
(n= 6–9, mean ± SD), * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

CONCLUSIONS

- **Severe RCB caused rapid vascular leakage and early mortality.**
- **MPLA preconditioning dramatically improved survival and attenuated early vascular leakage.**
- **KC contributed to RCB-associated vascular leakage and was reduced by MPLA.**
- **MPLA may serve as a pre-exposure MCM for personnel operating under a credible radiological threat.**

Additional findings:
MPLA also attenuated intestinal hyperpermeability and bacterial translocation after RCB.

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