Trauma Resuscitation: more than just blood products

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Traumatic injury
- Leading cause of death in patients under 40 years old
- Mechanisms of injury are quite diverse but include
  - Penetrating trauma
  - Blunt trauma
  - Orthopedic trauma
  - Neurologic trauma (usually bleeding in closed intracranial space but also includes more diffuse neuronal injury)
- All mechanisms may be associated with hemorrhage
- Many die within hours; survivors frequently develop severe inflammatory syndrome (SIRS) and/or infection
- SIRS or infection often lead to multisystem organ failure and death

The lethal triad

Hypoperfusion

Inflammation

Coagulopathy ↔ Hypothermia

Inflammation following trauma

Injury releases damaged cellular components that activate both innate immune cells and several other cell types via Toll-like receptors (TLR)

Distinct receptors respond to damaged components of infectious organisms (Pathogen Associated Molecular Patterns) and eukaryotic mitochondria (Damage Associated Molecular Patterns)
Inflammation following trauma

Injury upregulates both pro- and anti-inflammatory mediators

- TNF-α
- IL-6
- IL-1
- DAMP/PAMP
- IL-10
- IL-4
- IL-5
- aPC

Immunomodulation in trauma

- Most trials have resulted in either change or worsening survival
  - Examples include corticosteroids and antibodies against TNF-α
  - Some success, however, with estrogen therapy in male mice
- Major hurdles for research include:
  - the lack of understanding of the kinetics of inflammation in trauma: what do you inhibit? when do you inhibit it?
  - the complex nature of most trauma cases: what injury is the biggest determinant of outcome? How do transfusion, mechanical ventilation and other interventions influence outcome?
  - How does the presence of both sterile inflammation and infection influence outcome?

  **Approach: utilize short-acting, targeted anti-inflammatory drugs in models of sterile inflammation**

Kinetics of the inflammatory response

Hypothesis: appropriate modulation of the immune response to injury, at the appropriate time, may improve outcome

Curr Opin Anes 2011; 24: 219-223

Potency and Selectivity of SW Series

<table>
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<tr>
<th>R</th>
<th>IC50 (µM)</th>
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<tr>
<td>SW14 3-fluoro-4-hydroxyphenyl</td>
<td>85</td>
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<tr>
<td>SW20 4-hydroxyphenyl</td>
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<tr>
<td>SW23 3,5-di-fluoromethylphenyl</td>
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<td>SW30 Hydroxypropynyl</td>
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<td>PK36 H</td>
<td>&gt;100</td>
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Chem Biol 2010; 17: 123
In vivo efficacy: Miles assay

- Inject inhibitors 30 mg/kg IP in male rats
- One hour later inject VEGF subcutaneously on both flanks, followed by Evans blue dye IV
- Score dye extravasation on both flanks after one hour

Model of trauma-hemorrhage

Developed by Ayala and coworkers to simulate massive trauma in mice and rats

Protocol
1. Induce general endotracheal anesthesia
2. Perform exploratory laparotomy
3. Insert femoral arterial catheter and hemorrhage to achieve MAP = 40 mm Hg (normal MAP = 100 mm Hg)
4. After 60 min resuscitate with crystalloid (4x shed volume)
5. Follow for 6-24 hrs

Hypothesis: PI3Kγδ inhibition, if given at the proper time, will improve outcome

Trauma-hemorrhage resembles human injury

Evidence of organ inflammation at 24 hrs

- Tissue hypoperfusion (increased lactate/base deficit)
- Coagulation abnormalities (increased PTT/aPC); only see if both hypoperfusion and hemorrhage present
- Signs of inflammation (inflammatory cytokines, organ edema, neutrophil activity)
Pre-treatment with SW14 increases early mortality

Give SW14 (30 mg/kg) or saline prior to intubation

Post-treatment improves survival

Give SW14 (30 mg/kg) or saline vehicle 2 hrs following resuscitation

Post-treatment effect on systemic cytokines at 6 hrs

End-organ effects of SW14 at 24 hrs
**Possible synergy between inhibitor and aPC?**

- **aPC** has anticoagulant and anti-inflammatory properties
- aPC mediates anti-inflammatory function via PAR-1/EPCR, which is dependent on both MAPK/PI3K (beta or gamma)
- Perhaps a critical level of immune response (ROS/cytokines such as TNF-α) is required for aPC generation, which then synergizes with immune suppression of inhibitor?

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**Tibia fracture – rod placement model**

Mouse and rat model mimics human hip fracture and repair

Protocol:
1. induce general anesthesia (no intubation needed)
2. administer buprenorphine
3. fracture tibia, insert rigid needle to stabilize fracture
4. close incision and evaluate

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**Fracture increases cytokine levels but not PTT**

Niccolo Terrando, Mervyn Maze
PNAS 2010 107(47):20518-22
Ann Neurol. 2010 68(3):360-8
Conclusions

- Perioperative trauma care is a complex and evolving process
  - initial treatment includes surgical control of bleeding, repair of injury and resuscitation
  - often treatment goals will depend on the type of trauma (talks by Professors Junil Tang and Andre Campbell)
  - we are now beginning to appreciate how this care should also involve careful consideration of the inflammatory responses to injury, surgery and infection

- Dual PI3Kγ/δ inhibitors, when given appropriately, reduce inflammation and improve outcome in animal models of both trauma-hemorrhage and orthopedic injury
  - these agents may have utility in select trauma and operative patients, but further investigation into mechanism and patient selection are paramount

Resources for advancing knowledge

- Founded in 2008
- Stimulates interaction among existing, NIH-funded programs and fosters partnerships between academia, industry, and the community
- Designed to promote clinical and basic science studies to improve outcomes for critically ill or injured patients
Acknowledgements

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