PAMPs, DAMPs and our evolving understanding of Sepsis and SIRS

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**Systemic Inflammatory Response Syndrome (SIRS)**

≥ 2 of the following:

- Temp >38°C, <36°C
- Pulse >90
- RR >20, PCO2 <32
- WBC >12,000, <4000 or >10% bands

Inflammatory response to illness of **any** source

**Burden of SIRS**

1/3 of all hospitalized patients

- More than half of all ICU patients
- Nearly **all** SICU patients
- Morbidity and mortality 2° organ failure

- **Lung (ALI / ARDS)** > liver/kidney
Inflammation can reflect Infection or ‘Sterile SIRS’

Hemoperitoneum vs bacterial peritonitis

Aspiration vs bacterial pneumonia

Mechanistic understanding of SIRS

Infection

Fractures

Cytokines

‘DANGER’ molecules
**In non-infective conditions**

![Diagram showing innate immunity and innate immune responses to injuries like infection, shock, trauma, and fractures.]

**Innate immunity**

- **Ancient** (invertebrates, multi-celled)
  - PMN, Mφ, DC, NKC
- **No clonal expansion**
  - PRR on germ-line (TLRs, GPCRs)
  - multi-functional
- **Immediate response to danger motifs**
- **Rapid responses in trauma, sepsis**
PAMPs

Exogenous *infective* motifs

(LPS, FPs, bacterial sugars, ‘CpG’ DNA, dsRNA, flagellin…)

- Bind PRRs → immune activation
  → Cytokines etc
- Symptomatic infective SIRS (“sepsis”)
  ↑ NO• release → vasodilatation
  ↑ PMN-EC interactions → capillary leak

?? DAMPs…

*Non-infective* motifs

? *Endogenous* products of tissue injury
? Intracellular motifs released by mechanical injury
? Membrane motifs changed by toxins
? New motifs 2’ to metabolic, I/R stress

*Bind PRRs* → *immune activation*
*Cytokines etc*

?? …symptomatic *non-infective* SIRS
Intracellular DAMPs

Putative DAMP | PRR
--- | ---
HMGB-1 | TLR4
S-100 | RAGE
HSP 30/60 | TLR4
B7-H3 | TREM

- Few known
- Signal through PRR’s like PAMPs

Mitochondria as DAMPs

...why are clinical sepsis and SIRS so often indistinguishable?

- Mitochondria were saprophytic bacteria
  - Became endo-symbionts
  - Evolved into organelles
- ?‘Septic’ response to MT?
Do mitochondria contain DAMPs?

- 13 ‘endogenous’ peptides
  - begin with n-formyl-met
  - ? Do they activate FP receptors
- ‘Bacteria-like’ DNA
  - Unmethylated ‘CpG’ repeats
  - ? Do they activate TLR-9

Does mechanical tissue injury cause circulation of mitochondrial debris? (MTD)
mtDNA circulates after blunt trauma

Do shock / ischemia-reperfusion injury result in circulation of MTD?

Zhang, Hauser, Nature 2010
**Plasma mtDNA in rat HS**

![Graph showing mtDNA levels in rats](image)

mtDNA (µg/ml)

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*P<0.01 vs vol plasma (ANOVA)

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**mtDNA appears in plasma of FFx patients**

![Graph showing mtDNA levels in FFx patients](image)

Plasma Cyto B in Femur Fx

- Volunteer Plasma
- Patient Plasma
- Reaming Fluid

2^{14} -fold increase

*P<0.01 vs vol plasma (ANOVA)
Do MTD activate inflammatory cell signaling?

mtFPs activate $[\text{Ca}^{2+}]_i$ (via FPR1)

Zhang, Hauser, Nature 2010
mtDNA activates p38 via TLR9

TLR9 blocked by CQ, ODNs

Does MTD activate inflammatory cell phenotypes?

mtDNA activates p38 via TLR9

Zhang, Hauser, Nature 2010
MTD activates cytokine production

mtDNA activates PMN / EC interactions

Zhang, Hauser Nature 2010
Do mitochondrial DAMPs activate innate immunity in vivo?

MTD → PMN attack on lung

MMP-8 in lung

PMN in BALF

Zhang, Hauser Nature 2010
MTD causes ALI

Zhang, Hauser Nature 2010

MTD causes ALI

Zhang, Hauser Nature 2010
MTD ALI is oxidant-related

4-HNE stains

Zhang, Hauser Nature 2010

Evolutionary conservation of PAMPs and DAMPs in bacteria and mitochondria cause many similarities between sepsis and SIRS

Nature editorial March 4, 2010
**So what is ‘septic’ SIRS?**

PAMPs from infection cause SIRS

**What is non-infectious SIRS?**

2° Sepsis *perpetuates* SIRS → MOF → death
Treatment of *infective* SIRS

1) Remove PAMPs (bio-markers)
   - Antibiotic Tx
   - Drainage, source control
2) Rx SIRS *after* source control
   - Target PRR, signal cascades
   - Steroids, aPC, anti-cytokine Tx
   - (All *dangerous* w/o source control)

Treatment of *endogenous* SIRS

1) Remove DAMPs (bio-markers)
   - *Debride / drain* sources
   - *Avoid* antibiotics
2) *Prevent / treat SIRS* *early*
   - Target DAMPs and PRR
   - Interrupt inflammatory signaling
   - Safe w/o infection (*but ??healing*)
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