PAMPs, DAMPs and our evolving understanding of Sepsis and SIRS

Carl J. Hauser MD, FACS, FCCM

Gulf War Subcommittee

Beth Israel Deaconess Medical Center

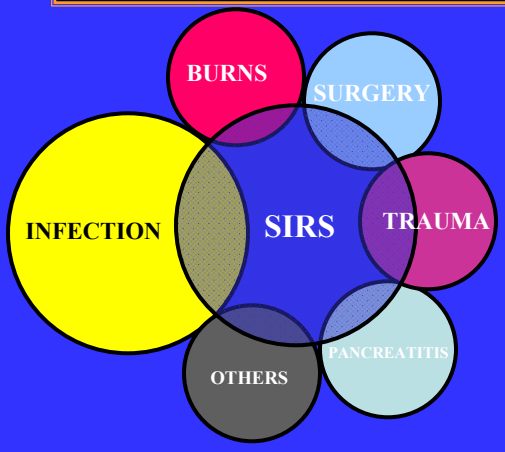
Harvard Medical School

Disclosures / Competing interests

FUNDING

- NIH
- DoD (CDMRP)
- CIMIT
- No commercial funding

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

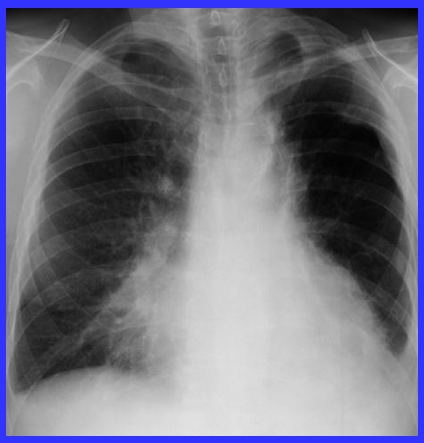
Burden of SIRS

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

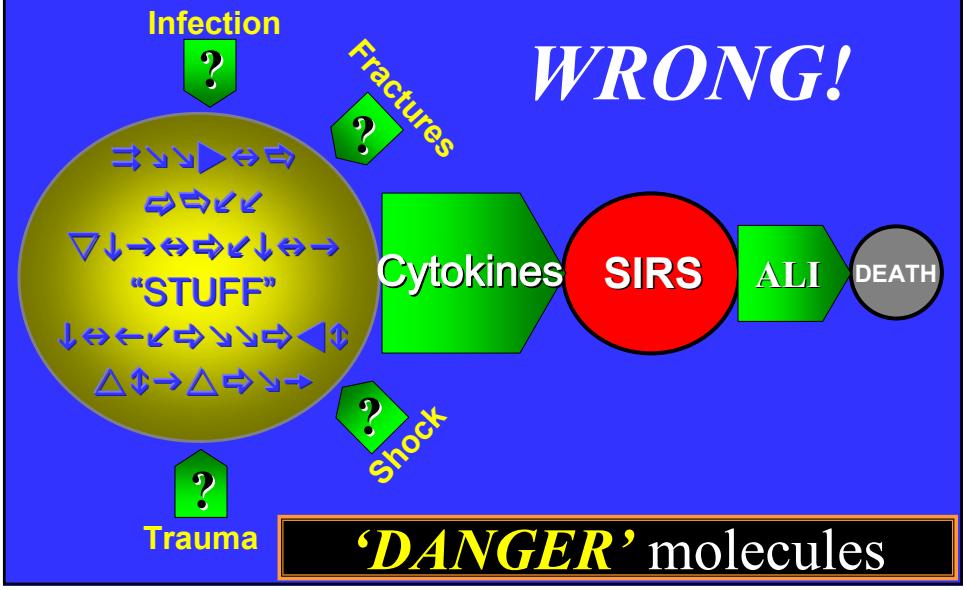
Inflammation can reflect Infection or 'Sterile SIRS'

Hemoperitoneum ***vs*** bacterial peritonitis

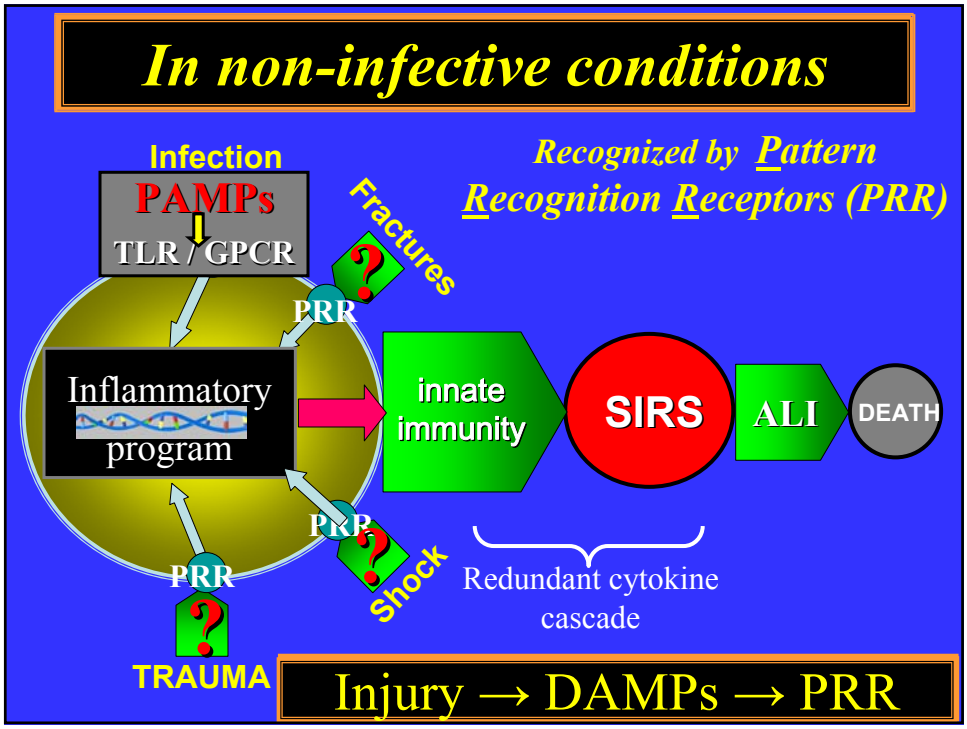


Aspiration ***vs*** bacterial pneumonia

Mechanistic understanding of SIRS



'DANGER' molecules



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?

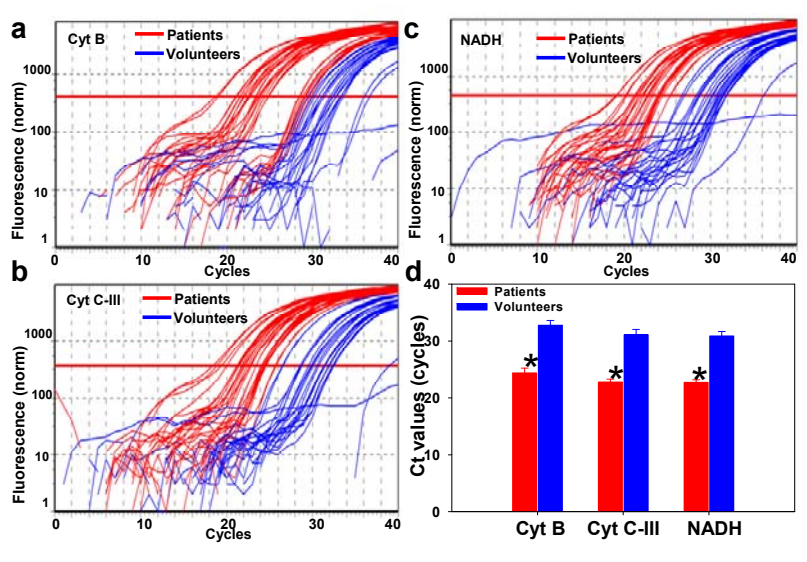
- Mitochondria were saprophytic bacteria
  - ✓ Became endo-symbionts
  - ✓ Evolved into organelles
- ***?'Septic' response to MT?***

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)

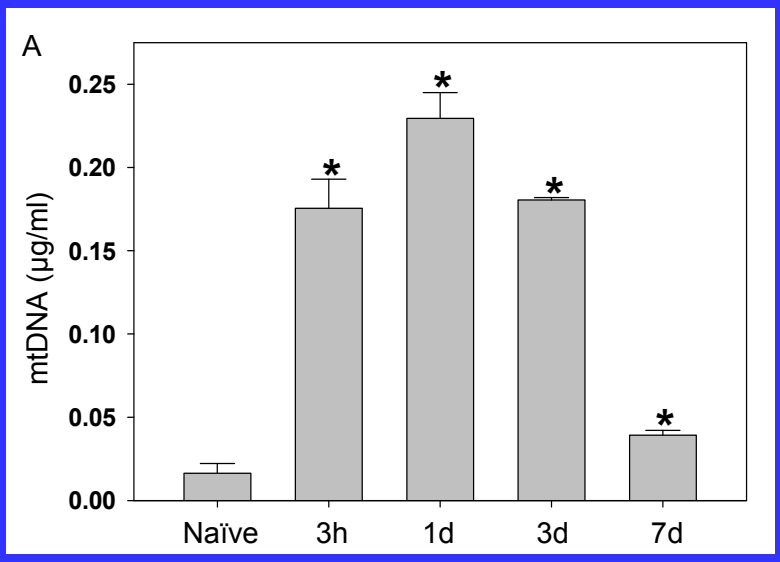
mtDNA circulates after blunt trauma



Zhang, Hauser , Nature 2010

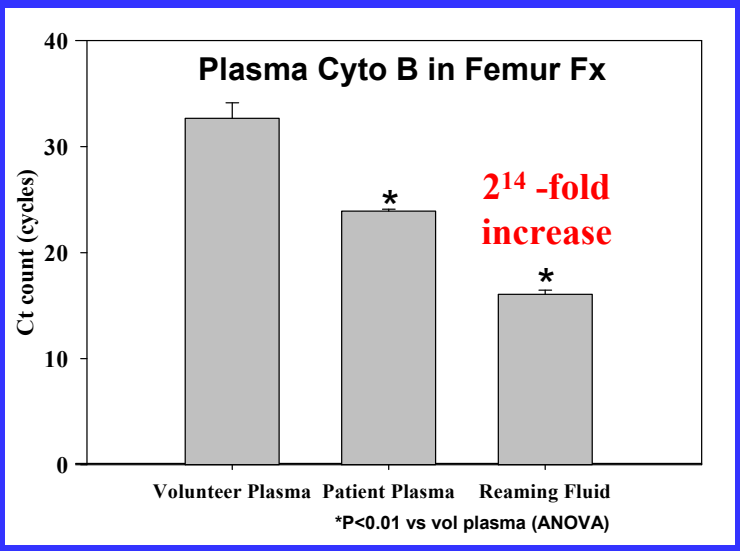
Do shock / ischemia-reperfusion injury result in circulation of MTD ?

Plasma mtDNA in rat HS



Zhang, Hauser; Shock 2010

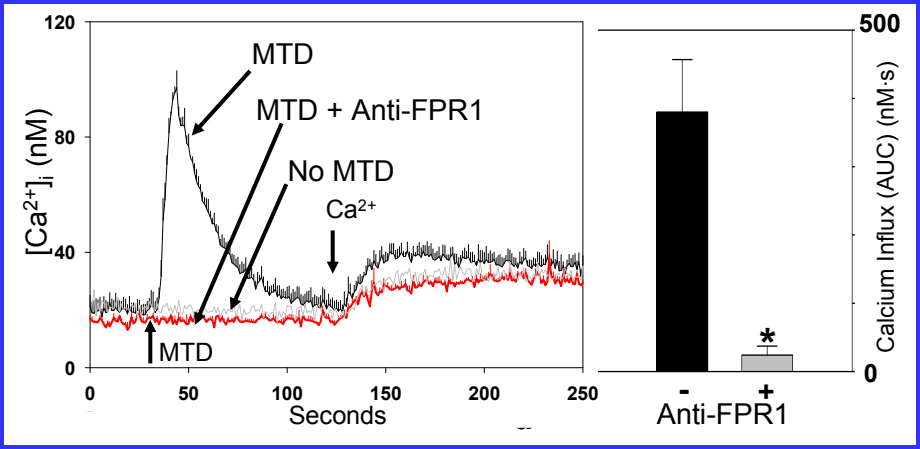
mtDNA appears in plasma of FFx patients



Hauser, J Ortho Trauma 2010

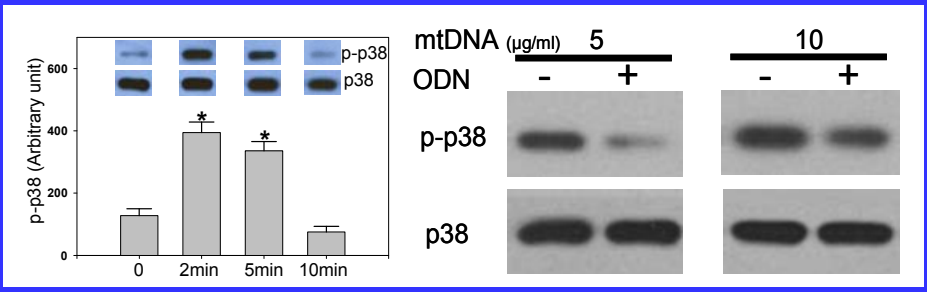
Do MTD activate inflammatory cell signaling ?

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



Zhang, Hauser , Nature 2010

mtDNA activates p38 via TLR9

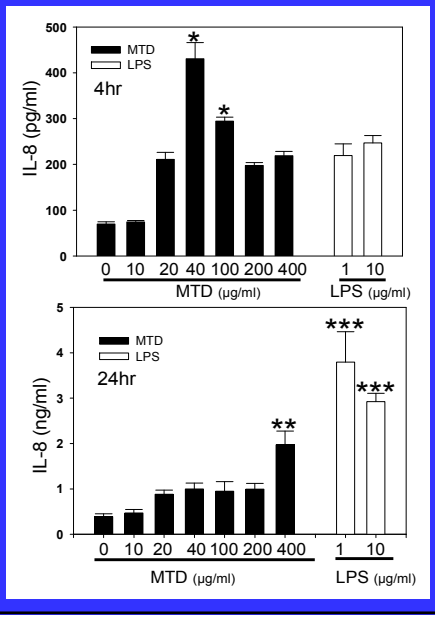


TLR9 blocked by CQ, ODNs

Zhang, Hauser , Nature 2010

Does MTD activate inflammatory cell phenotypes ?

MTD activates cytokine production

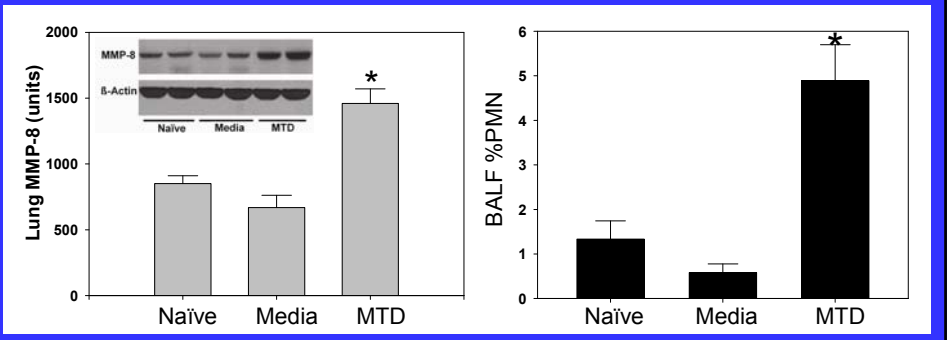


Zhang, Hauser *Nature* 2010

mt**DNA** activates PMN / EC interactions

Do mitochondrial DAMPs activate innate immunity in vivo?

MTD → PMN attack on lung

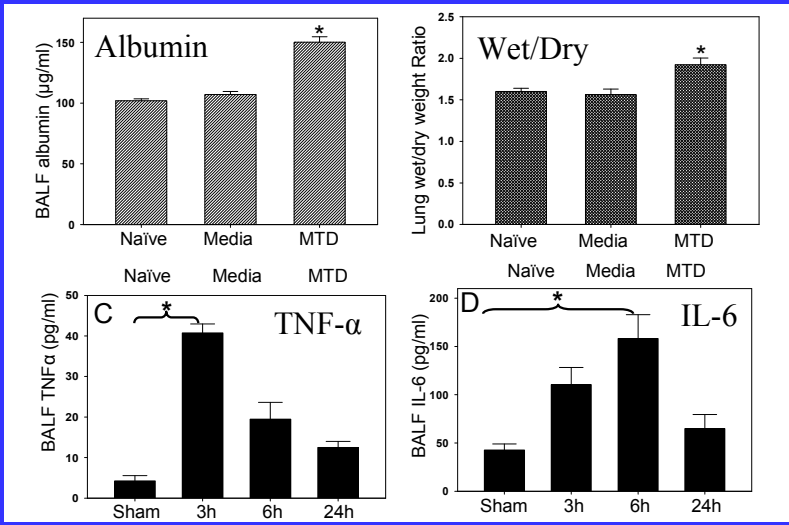


MMP-8 in lung

PMN in BALF

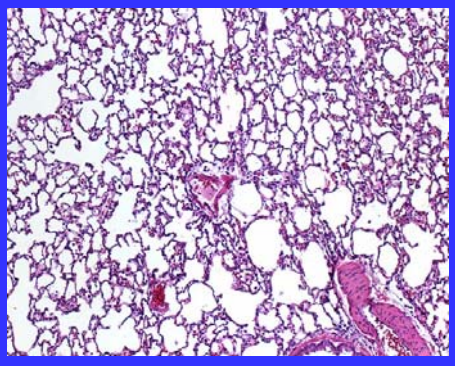
Zhang, Hauser *Nature* 2010

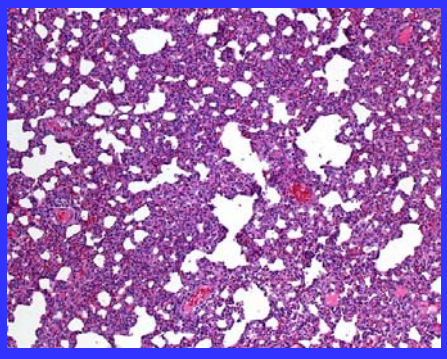
MTD causes ALI



Zhang, Hauser *Nature* 2010

MTD causes ALI



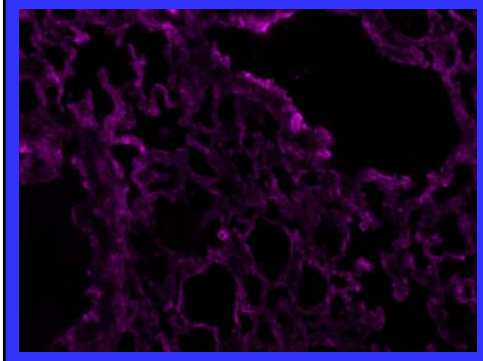


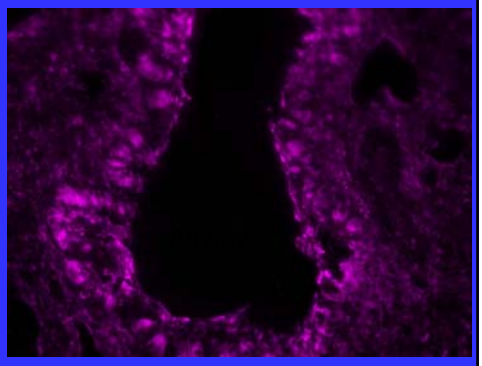
Sham

i.v. MT (=5% liver injury) at 6h

Zhang, Hauser *Nature* 2010

MTD ALI is oxidant-related



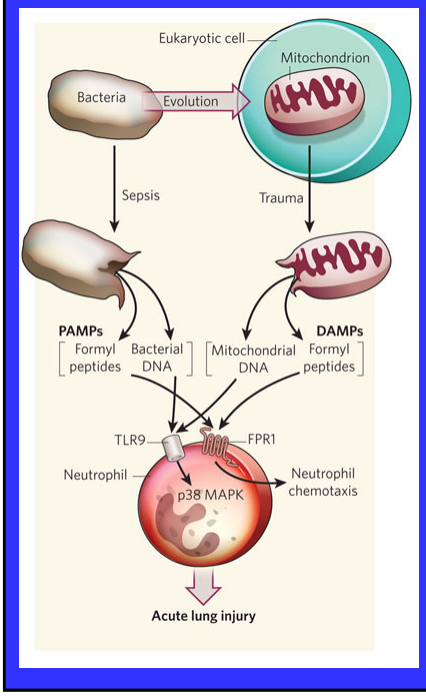


Media

MTD

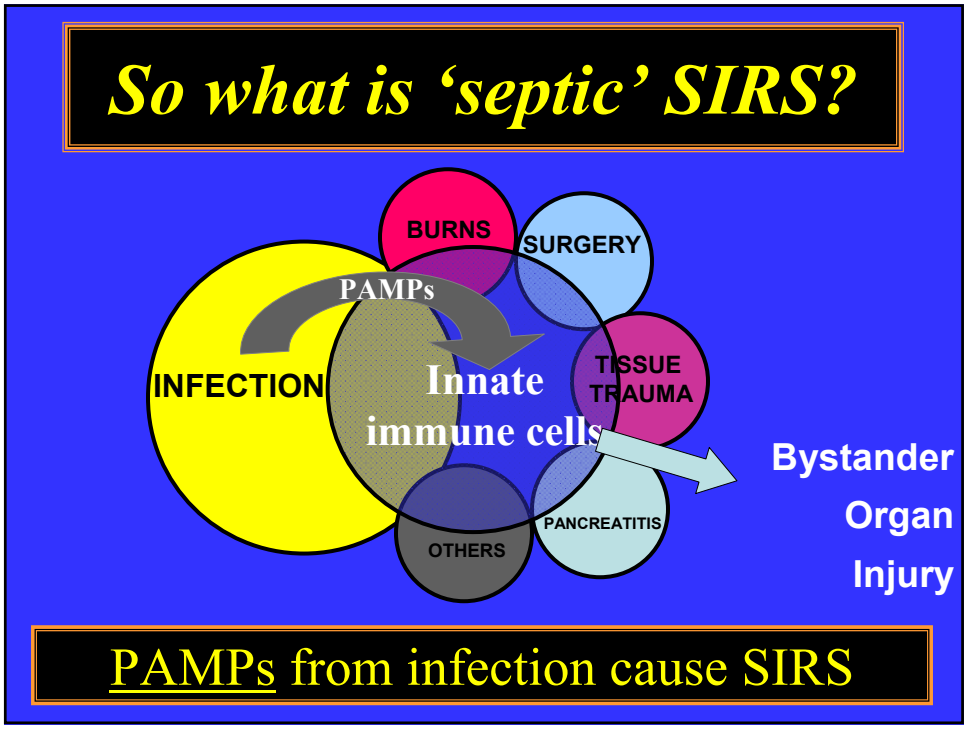
4-HNE stains

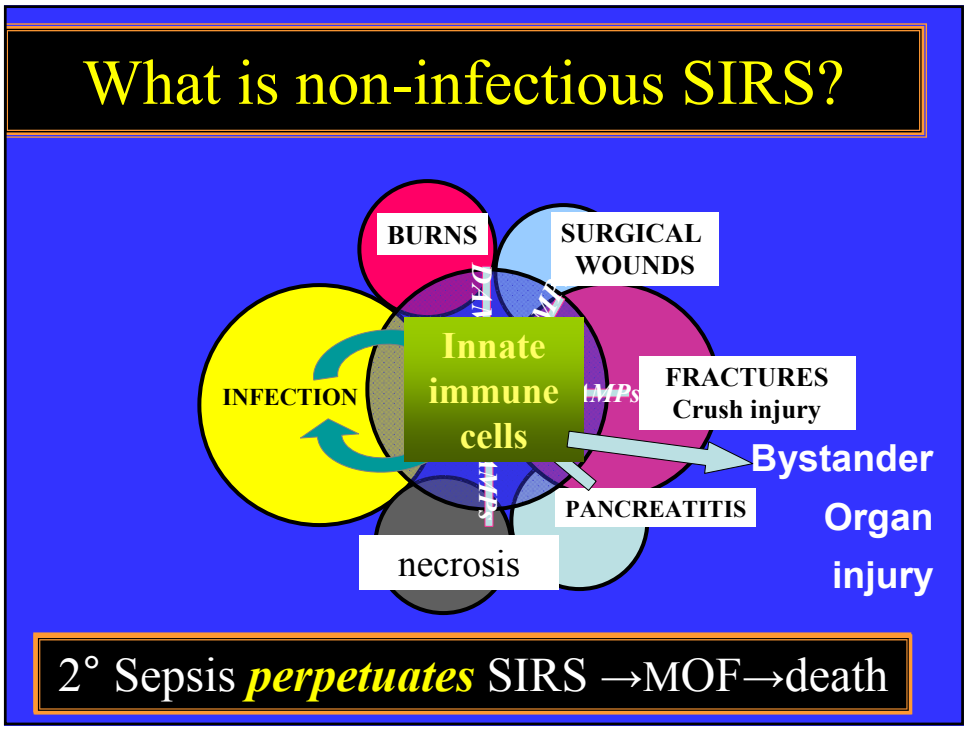
Zhang, Hauser *Nature* 2010



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?
BURNS
SURGERY
PAMPs
INFECTION
Innate immune cells
TISSUE TRAUMA
PANCREATITIS
OTHERS
Bystander Organ Injury
PAMPs from infection cause SIRS


What is non-infectious SIRS?
BURNS
SURGICAL WOUNDS
INFECTION
Innate immune cells
FRACTURES Crush injury
PANCREATITIS
necrosis
Bystander Organ injury
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*)

Acknowledgements

Hauser Lab

Kiyoshi Itagaki

Qin Zhang

Mustafa Raoof

Tolga Sursal

Junger Lab

Yu Chen

Yuka Sumi

London

Karim Brohi