Host response: septic versus non-septic

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Basic implications

Is the response to infection so specific?

1) Is there a rationale to believe that the response to infection is not specific?

2) Is there evidence that the response to infection is not specific?
Host Response to Sepsis

Pattern recognition receptors

Pathogen associated molecular patterns

Balanced response
Pathogen elimination
Tissue recovery

Unbalanced response
Hyperinflammation
Tissue injury
Immune suppression
Host Response to Sepsis

Pathogen associated molecular patterns

Damage associated molecular patterns

Pattern recognition receptors

Balanced response

Pathogen elimination
Tissue recovery

Unbalanced response

Hyperinflammation
Tissue injury
Immune suppression

HSPs
Fibrinogen
Hyaluronan
Biglycan
HMGB1
DNA
RNA
IL-1α, IL-33
S100 proteins
Four classes of pattern-recognition receptors
Damage associated molecular patterns triggering TLR signaling

<table>
<thead>
<tr>
<th>DAMP</th>
<th>Toll-like receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat shock proteins</td>
<td>TLR4</td>
</tr>
<tr>
<td>HMGB1</td>
<td>TLR4</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>TLR4</td>
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<tr>
<td>S100A8/9</td>
<td>TLR4</td>
</tr>
<tr>
<td>Extracellular DNA</td>
<td>TLR9</td>
</tr>
<tr>
<td>Extracellular RNA</td>
<td>TLR3</td>
</tr>
<tr>
<td>Hyaluronan</td>
<td>TLR4/TLR2</td>
</tr>
<tr>
<td>Biglycans</td>
<td>TLR4</td>
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</tbody>
</table>
S100A8/9 expression in patients with community-acquired pneumonia

Achouiti A et al. Thorax 2014; 69: 1034
Acute lung injury is associated with elevated S100A8/9 levels in bronchoalveolar lavage fluid

Kuipers MT et al. PLoS One 2013; 8: e68694
Interaction between S100A8/9 and TLR4: an autocrine positive feedback loop

Adapted from Vogl & Roth
S100A9 contributes to pulmonary protein leak upon exposure to LPS and mechanical ventilation

MV = mechanical ventilation

Kuipers MT et al. PLoS One 2013; 8: e68694
Nucleosomes are the “DNA packaging units” in eukaryotes.

DNA segment wound around eight histone protein cores.
Circulating nucleosomes in children with meningococcal sepsis

[Graph showing nucleosome levels over time for non-survivors and survivors]
Circulating nucleosomes and histones in trauma patients

Abraham ST. AJRCCM 2013; 187: 160
DNA release in the airways of mice with MRSA pneumonia

Anne Jan van der Meer [unpublished]

Host DNA

MRSA DNA

Nucleosome levels

0h 6h 24h 48h 72h

U/ml

100000
10000
1000
100
10
1

ng/ml

5000
4000
3000
2000
1000
0

0.4
0.3
0.2
0.1
0.0

6h 24h 48h

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Administration of an anti-histone 4 antibody protects against LPS-induced lethality

<table>
<thead>
<tr>
<th>Hours</th>
<th>% survival</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
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<tr>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

P = 0.004

LPS only
LPS + anti-H4 antibody

Neutralization of extracellular histones protects against liver ischemia-reperfusion injury

Serum ALT

Extent of necrosis

Huang H. Hepatology 2011; 54: 999
Extracellular histones mediate liver ischemia-reperfusion injury through Toll-like receptor 9

Exogenous histone administration

Anti-histone antibodies

Huang H. Hepatology 2011; 54: 999
TLR9 deficient mice are protected against death due to polymicrobial sepsis.

**Survival**

- TLR9\(^{-/-}\)
- WT

**Cytokine response**

- TNF pg/ml serum
- MCP-1 ng/ml serum
- IL-6 ng/ml serum
- IL-10 ng/ml serum

*P* < 0.001
Is the response to infection so specific?

What about the systemic genomic response?

DAMPs are released during infection and sterile injury, and cause damage via similar mechanisms.
The genomic response in postoperative patients with abdominal sepsis and sterile surgery is largely similar.

- Expression of 86% of all genes altered in abdominal sepsis
- 70% of the genomic response to sepsis similar to response after abdominal surgery

Scicluna B. et al. [unpublished]
The genomic response in postoperative patients with abdominal sepsis and sterile surgery is largely similar.

**Common pathways over-expressed**

- Integrin Signaling
- Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes
- IL-10 Signaling
- Hypoxia Signaling in the Cardiovascular System
- IL-1 Signaling
- TREM1 Signaling
- IL-8 Signaling
- Toll-like Receptor Signaling
- iNOS Signaling
- IL-6 Signaling

**Common pathways under-expressed**

- EIF2 Signaling
- Regulation of eIF4 and p70S6K Signaling
- mTOR Signaling
- iCOS-iCOSL Signaling in T Helper Cells
- tRNA Charging
- CD28 Signaling in T Helper Cells
- Role of NFAT in Regulation of the Immune Response
- Calcium-induced T Lymphocyte Apoptosis
- Natural Killer Cell Signaling
- T Cell Receptor Signaling

Scicluna B. et al. [unpublished]
Genomic changes associated with severe blunt trauma

Up-regulated Pathways

- Integrin Signaling
- Leukocyte Extravasation
- Fcγ Receptor Mediated Phagocytosis
- IL-10 Signaling
- Toll-like Receptor Signaling
- Ephrin Receptor Signaling
- IL-6 Signaling
- TREM1 Signaling
- Actin Cytoskeleton Signaling
- B cell Receptor Signaling

Down-regulated Pathways

- Ca2+ T cell Apoptosis
- iCOS-iCOSL Signaling in T cells
- CTLA4 Signaling in CD8 T cells
- CD28 Signaling in T cells
- T cell Receptor Signaling
- CD8 T Cell Mediated Apoptosis
- Role of NFAT in Immune Response
- IL-4 Signaling
- Primary Immunodeficiency Signaling
- Purine Metabolism
Is the response to infection so specific?

1) Is there a rationale to believe that the response to infection is not specific?

1) YES: PAMPs and DAMPs largely activate the same receptors and pathways

2) YES: In accordance, the host response to severe infection and sterile injury is quite similar

2) Is there evidence that the response to infection is not specific?
The injurious host response to trauma and infection

- Penetrating trauma
- Thermal injury
- Blunt trauma
- Tissue damage
  - DAMPs
    - mtDNA
    - Formyl peptides
    - HMGB1
    - CIRP
    - F-actin
  - PAMPs
    - Endotoxin
    - Flagellin
    - dsRNA
    - Peptidoglycan

- Complement
- Neutrophils
- Monocytes
- γδT cells
- Plasmacytoid dendritic cells
- Dendritic cells

Proinflammatory and anti-inflammatory cytokines
- TNFα
- Interleukin-8
- G-CSF
- Interleukin-10
- Interleukin-12p40
- Interleukin-1α/β
- Interleukin-1ra
- MCP-1

Tissue damage → Endothelial and organ damage

Immunoparesis → Sepsis

Lord JM et al. Lancet 2014; 384: 1455
“Persistent Inflammation Immunosuppression and Catabolism Syndrome” (PICS)

CCI = chronic critical illness

Vanzant EL. J Trauma Acute Care Surgery 2014; 76: 21
The Host response to Sepsis

**Theory 1**
- Early deaths due to overwhelming inflammation
- Late deaths due to persistent immunosuppression and recurrent infections

**Theory 2**
- Early deaths due to overwhelming inflammation
- Late deaths due to intractable inflammation-induced organ injury
The host response during severe sepsis and after severe non-infectious injury shows a strong resemblance, and is characterized by concurrent “hyper-inflammation” and immune suppression.

Patients who remain in need of intensive care enter a state of chronic critical illness characterized by cellular malfunction, non-resolving inflammation and immune suppression.