ICU-acquired immunosuppression

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An unusual nosocomial pneumonia

2008/08: a 62 y.o. woman is admitted to the ICU for septic shock

- No significant past-medical history
- Recently: asthenia, fever and increasing abdominal pain
- Temperature 40°C; HR 125; BP 74/45; RR 38
- CT scan: complicated diverticulitis
- Intraoperative findings: fecal peritonitis

Clinical course:
- MOF (Shock, ARDS, ARF, DIC, Lactic acidosis)
- Day 12: ventilator-associated pneumonia; A. fumigatus
- Outcome: death (2-month ICU stay)

Final diagnosis: invasive aspergillosis
Sepsis-induced immunosuppression

Net immunological response in sepsis

Proinflammatory response

Immune activation

Homeostasis

Immune suppression

Viral reactivation

Anti-inflammatory response

Death

Time (days)

Hotchkiss, Nature Med 2009
Herpes Simplex Virus Lung Infection in Patients Undergoing Prolonged Mechanical Ventilation

Charles-Edouard Luyt\textsuperscript{1}, Alain Combes\textsuperscript{1}, Claire Deback\textsuperscript{2}, Marie-Hélène Aubriot-Lorton\textsuperscript{3}, Ania Nieszkowska\textsuperscript{1}, Jean-Louis Trouillet\textsuperscript{1}, Frédérique Capron\textsuperscript{3}, Henri Agut\textsuperscript{2}, Claude Gilbert\textsuperscript{1}, and Jean Chastre\textsuperscript{1}

- HSV bronchopneumonitis in 42 of 201 pts who deteriorated, with a mean MV duration before diagnosis of 14±6 days.

- Risk factors: oral–labial lesions, HSV in the throat, and macroscopic bronchial lesions seen during bronchoscopy.

- Patients with HSV bronchopneumonitis had complicated courses, with

\[ \begin{align*}
238 & \text{ventilated} \\
& \geq 5 \text{ days} \\
& \rightarrow 34 \text{ not included} \\
& 25 \text{ received IS/CS} \\
& 5 \text{ neutropenic} \\
& 3 \text{ had AIDS} \\
& 1 \text{ pregnant} \\
& \rightarrow 204 \text{ eligible} \\
& \rightarrow 3 \text{ were clinically stable and not evaluated for HSV} \\
& \rightarrow 201 \text{ evaluated for HSV} \\
& \rightarrow 109 (54\%) \text{ with HSV}^+ \text{ OPS} \\
& \rightarrow 92 (46\%) \text{ with HSV}^\text{−} \text{ OPS} \\
& \rightarrow 98 (90\%) \text{ with HSV}^+ \text{ BAL} \\
& \rightarrow 11 (10\%) \text{ with HSV}^\text{−} \text{ BAL} \\
& \rightarrow 31 (34\%) \text{ with HSV}^+ \text{ BAL} \\
& \rightarrow 61 (66\%) \text{ with HSV}^\text{−} \text{ BAL} \\
& \rightarrow 38 (39\%) \text{ with HSV BPn} \\
& \rightarrow 60 (61\%) \text{ without HSV BPn} \\
& \rightarrow 4 (13\%) \text{ with HSV BPn} \\
& \rightarrow 27 (87\%) \text{ without HSV BPn}
\end{align*} \]
Sepsis-induced immunosuppression
Sepsis-induced immunosuppression

- Decreased production of proinflammatory & immunostimulatory cytokines (IL-1, TNF-α, IL-12)
Sepsis-induced immunosuppression

- Decreased production of proinflammatory & immunostimulatory cytokines (IL-1, TNF-\(\alpha\), IL-12)

- Increased IL-10 production
  Kell, Shock 1999
Sepsis-induced immunosuppression

- **Decreased production of proinflammatory & immunostimulatory cytokines (IL-1, TNF-\(\alpha\), IL-12)**

- **Increased IL-10 production**
  Kell, Shock 1999

- **Apoptosis of T & B lymphocytes**
Sepsis-induced immunosuppression

- Decreased production of proinflammatory & immunostimulatory cytokines (IL-1, TNF-\(\alpha\), IL-12)

- Increased IL-10 production
  Kell, Shock 1999

- Apoptosis of T & B lymphocytes

- Relative increase in regulatory T-cells
  Monneret, Crit Care Med 2003
INFECTION

Bacteria

Complement system

Defensins

Lipoproteins

DNA

Outer membrane protein

Peptidoglycan

Fimbriae

Lipopolysaccharide

Lipopolysaccharide binding protein

sCD14

Endothelial cells

Neutrophils

Mast cells

Epithelial cells

Monocytes/macrophages

Toll-like receptor

PGRP

Dendritic cells

Lymphocytes

Monocytes/macrophages

C5a

Tissue factor

Coagulation

Pro-inflammatory mediators

TNF

Interleukin 1

NO...

Inflammation

Moderate: beneficial alarm signal

Severe: deleterious effects

Organ dysfunction

Anti-inflammatory mediators

Interleukin 10 and interleukin 1Ra

and sTNFR

Immunity: immune depression

Inflammation: down-regulation

Increased susceptibility to nosocomial infection

Annane, Lancet 2005
Sepsis-induced immunosuppression

- Decreased production of proinflammatory & immunostimulatory cytokines (IL-1, TNF-\(\alpha\), IL-12)

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  Kell, Shock 1999

- Apoptosis of T & B lymphocytes

- Relative increase in regulatory T-cells
  Monneret, Crit Care Med 2003

- **Monocyte deactivation and reduced HLA-DR expression**
  Docke, Nat Med 1997 & Caille, Shock 2004
Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock

![Diagram showing cell populations and their expression of FITC-CD14 and PE-HLA-DR](image)

- **a** FITC-CD14
  - **Non-survivor**: 21%
  - **Survivor**: 43%
  - **Healthy donor**: 93%

- **b** PE-HLA-DR
Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock

![Graph showing the relationship between mHLA-DR expression and mortality in septic shock. The graph depicts a Kaplan-Meier survival curve with two lines: one for mHLA-DR > 30% and another for mHLA-DR ≤ 30%. The log rank test shows a statistically significant difference between the two groups, with a p-value of 0.0006. The number of subjects remaining at risk is also shown for each group at different time points.]

Number remaining at risk:
- mHLA-DR > 30%: 49, 49, 45, 43, 39, 35, 31
- mHLA-DR ≤ 30%: 37, 34, 30, 25, 21, 18, 14
Low monocyte human leukocyte antigen-DR is independently associated with nosocomial infections after septic shock.
Lack of recovery in monocyte human leukocyte antigen-DR expression is independently associated with the development of sepsis after major trauma

Aurélie Cheron¹, Bernard Floccard¹, Bernard Allaouchiche¹, Caroline Guignant², Françoise Potevin², Christophe Malcus³, Jullien Crozon¹, Alexandre Faure¹, Christian Guillaume¹, Guillaume Marcotte¹, Alexandre Vulliez¹, Olivier Monneuse⁶, Guillaume Monneret²

Sepsis prediction

Developed sepsis

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mHLA-DR (AB/C) vs Days post-trauma

1-2  | 3-4  | 5-6  | 7-8  | 9-10 | 11-12

Developed sepsis

Sensitivity vs Specificity
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Cheron et al. Critical Care 2010, 14:R208
### Mouse Dendritic Cells subsets

<table>
<thead>
<tr>
<th>DC subsets</th>
<th>IFN-I production</th>
<th>Production of other microbicidal compounds (TNFα, NOIs, ROIs)</th>
<th>Cross-presentation</th>
<th>Other proposed functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT-DCs pDCs</td>
<td>+++</td>
<td>TNFα +++</td>
<td>+</td>
<td>Global orchestration of antiviral immune defenses, induction of tolerance, induction of regulatory T cells</td>
</tr>
<tr>
<td>CD8α⁺ DCs</td>
<td>+</td>
<td>+/-</td>
<td>+++</td>
<td>IL-12 production, induction of tolerance or immunity depending on danger signals</td>
</tr>
<tr>
<td>CD11b⁺ DCs</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>MHC II antigen processing and presentation, induction of humoral immunity</td>
</tr>
<tr>
<td>Skin mig-DCs</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Induction of tolerance or immunity depending on danger signals</td>
</tr>
<tr>
<td>LCs*</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>CD207⁺CD103⁺ DDCs</td>
<td>?</td>
<td>?</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>CD207⁻ DDCs⁺ inf-DCs</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>MHC I and II processing and presentation of pathogen-derived antigens</td>
</tr>
</tbody>
</table>

*Immunological Reviews 2010 Vol. 234: 177–198*
Dendritic Cells & Sepsis

- DCs contribute to efficient host defense mechanisms during polymicrobial sepsis

Scumpia, J Immunol 2005
CD11c⁺ Dendritic Cells Are Required for Survival in Murine Polymicrobial Sepsis¹

Philip O. Scumpia,* Priscilla F. McAuliffe,* Kerri A. O’Malley,* Ricardo Ungaro,* Takefumi Uchida,* Tadashi Matsumoto,* Daniel G. Remick, ‡ Michael J. Clare-Salzler, †
Lyle L. Moldawer, ‡* and Philip A. Efron*
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Lyle L. Moldawer,‡* and Philip A. Efron*

CLP model, transgenic mice (B6.FVB-Tg(.Itgax-DTR/EGFP.57)Lan/J)
Dendritic Cells & Sepsis

• DCs contribute to efficient host defense mechanisms during polymicrobial sepsis
  Scumpia, J Immunol 2005

• Sepsis induces both a significant systemic and local apoptotic loss of DC cells in lymph nodes
  Efron, J Immunol 2004
Dendritic Cells & Sepsis

• DCs contribute to efficient host defense mechanisms during polymicrobial sepsis
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• DCs are depleted in septic patients
Human Dendritic Cells subsets

Conventional DCs (mDCs)

Plasmacytoid DCs (mDCs)
Profound and persistent decrease of circulating dendritic cells is associated with ICU-acquired infection in patients with septic shock

- 43 pts with septic shock
- Control cohorts: age-matched healthy volunteers (HV), non severe sepsis (S) & non septic shock (NSS)
- Trucount® kit (BD Bioscience)
- 100 µL of whole blood (Day 1, 3 & 7)
- Flow cytometry
  - Multiple immunostaining (6 mABs)
  - FACSCanto®
- Gating strategy
  - CD45 +, Lin -
  - mDCs : HLA-DR +, CD11c +
  - pDCs : HLA-DR +, CD 123 +
Circulating DCs are dramatically depleted at day 1 of septic shock.
Maturation of DCs is altered during septic shock

Profound and persistent decrease of circulating dendritic cells is associated with ICU-acquired infection in patients with septic shock.
Profound and persistent decrease of circulating dendritic cells is associated with ICU-acquired infection in patients with septic shock.

mDCs increase @ D7 in pts without secondary infection (SI)

A negative relative variation in mDCs between D7 & D1 is strongly associated with secondary infection OR 22 (2.53-191, $P=0.005$)
Dendritic Cells & Sepsis

• DCs contribute to efficient host defense mechanisms during polymicrobial sepsis
  Scumpia, J Immunol 2005

• Sepsis induces both a significant systemic and local apoptotic loss of DC cells in lymph nodes
  Efron, J Immunol 2004

• DCs are depleted in septic patients

• DCs might contribute to sepsis-induced immunosuppression
A mouse model of sublethal polymicrobial sepsis

Sham (n=19)

CLP+antibiotics (n=30)

CLP (n=12)

Impaired bacterial clearance

Subcutaneous & peritoneal abscesses @ D30
Sepsis Induces Functional Abnormalities of DCs

**Spleen DCs**
- Quick & transient depletion of CD8α + subset DCs
- Altered maturation of DCs
- Decreased IL-12 release
- Biphasic influence on the proliferation of allogenic T cells

**BMDCs**
- Profound alteration of DCs maturation
- TLRs agonists do not induce maturation of BMDCs
- Decreased production of IL-12
- Decreased proliferation of allogenic T cells
TLR signaling influences survival of DCs with minimal influence on maturation & activation processes.
Polymicrobial sepsis durably affects the functions of DCs
Polymicrobial sepsis durably affects the functions of DCs
Adoptive transfer of DCs improve survival to secondary *P. aeruginosa pneumoniae*
Adoptive transfer of DCs improve survival to secondary *P. aeruginosa pneumoniae*
Mice that survive to polymicrobial sepsis display major susceptibility to P. aeruginosa secondary pneumonia characterised by severe pulmonary inflammatory response and marked lung damage.

Adoptive transfer of DCs improves survival to secondary pneumonia in CLP mice.

DCs do not improve bacterial lung clearance but decrease systemic dissemination.

DCs modulate inflammatory response towards P. aeruginosa by delaying PMN recruitment and dampening the release of TNF-α while restoring efficient IL-12 production in CLP mice.
BMDCs restore the IL-12 / IL-10 balance during P. aeruginosa pneumonia in CLP mice

Sham-operated mice + PAO1  CLP mice + PAO1  CLP mice + PAO1 + BMDC

Sepsis-induced immunosuppression

Net immunological response in sepsis

- Proinflammatory response
- Immune activation
- Homeostasis
- Immune suppression
- Viral reactivation
- Death

Time (days)
Sepsis-induced immunosuppression

Can we change this?
Monocytic HLA-DR expression in intensive care patients: Interest for prognosis and secondary infection prediction

Anne-Claire Lukaszewicz, MD; Marion Grienay, MD; Matthieu Resche-Rigon, MD, PhD; Romain Pirracchio, MD; Valérie Faivre, PhD; Bernadette Boval, MD; Didier Payen, MD, PhD
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**Graph**: BAL pseudomonas + aspergillus fumigatum

- Days after ICU admission for septic shock (post-op peritonitis)

- Days 8 to 16:
  - Day 8: 500
  - Day 9: 280
  - Day 10 to 12: Increase
  - Day 13: 1500
  - Day 14: 2500
  - Day 15: 2000
  - Day 16: 3000

- Interferon γ injections indicated by arrows.

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*Crit Care Med 2009 Vol. 37, No. 10*
Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

A Double-Blind, Randomized, Placebo-controlled Multicenter Trial

Christian Meisel, Joerg C. Schefold, Rene Pschowski, Tycho Baumann, Katrin Hetzger, Jan Gregor, Steffen Weber-Carstens, Dietrich Hasper, Didier Keh, Heidrun Zuckermann, Petra Reinke, and Hans-Dieter Volk

monocytic HLA-DR required: ≤ 8,000 mAB/cell

dose escalation if monocytic HLA-DR < 15,000 mAB/cell

day 0

GMCSF-group: 4 µg/kg/day or 8 µg/kg/day
Placebo-group: 0.9% NaCl

A

8x10^3
6x10^3
4x10^3
2x10^3
0

study day

B

2000
1500
1000
500

study day

- Restore TLR-2 & TLR-4 mediated release of inflammatory cytokines
- Decrease IL-10 release
Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

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Christian Meisel1*, Joerg C. Schefold2*, Rene Pschowski2, Tycho Baumann1, Katrin Hetzger1, Jan Gregor3, Steffen Weber-Carstens3, Dietrich Hasper2, Didier Keh4, Heidrun Zuckermann3, Petra Reinke2,5, and Hans-Dieter Volk1,5
Conclusions - 1

- Sepsis is commonly associated with immune dysfunction characterized by
  - Imbalance of the pro-inflammatory/anti-inflammatory cytokine response
  - Apoptosis of immune cells
  - Down-regulation of monocytes HLA-DR expression
  - Functional abnormalities of dendritic cells
- Down-regulation of HLA-DR and depletion of circulating DCs during septic shock is associated with nosocomial infections
Conclusions - II

- Novel immuno-monitoring strategies are helpful to identify patients with sepsis-induced immunosuppression.

- Experimental and clinical evidence highlight a role of monocytes and DCs in sepsis-induced immunosuppression that might be targetable by novel immunotherapies.