Od PAMPs a DAMPs k biomarkerům sepse

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Imunopatogeneze sepse
Revisiting caspases in sepsis

M Aziz, A Jacob and P Wang
PAMPs a DAMPs
Host innate immune responses to sepsis.

**PAMPs**
- LPS
- LTA
- Lipopeptide
- Peptidoglycan
- Flagella
- DNA
- RNA

**DAMPs**
- HSPs
- Fibrinogen
- Hyaluronan
- Biglycan
- HMGB1
- DNA
- RNA
- IL-1α, IL-33
- MRP8/14

**PRRs**

**Septic response**
- Leukocyte activation
  - Cytokines
  - Proteases
  - Reactive oxygen species
  - NETs
- Complement activation
- Coagulation activation
- Necrotic cell death

**Impaired function of immune cells**
- Apoptosis of T, B and DCs
- Expansion of Tregs and myeloid suppressor cells
  - Impaired phagocytosis

**Neuroendocrine regulation**
- Inhibition of proinflammatory gene transcription
  - Anti-inflammatory cytokines
  - Soluble cytokine receptors
  - Negative regulators of TLR signaling
  - Epigenetic regulation

**Pro-inflammatory response**
- Excessive inflammation causing collateral damage (tissue injury)

**Immune suppression**
- Enhanced susceptibility for secondary infections and late mortality
Extrinsic pathway: Toll-like receptor


Intrinsic pathway: Nod-like receptor

Other substrates: proIL-18 Glycolysis Cytoskeleton Caspase7 etc.
Centrální role mitochondrií v patogenezi sepse?
Glucose homeostasis
- Insulin resistance/secretion
- Inhibition of glycolysis

Inflammation
- IL-1β
- IL-18, etc.

Systemic response Amplification

Autophagy/Mitophagy
Terapia
zasahovat?

- komplikované vztahy
- unikátní jedinci
- unikátní kombinace patogen + hostitel
- akce + reakce
- proteáza + antiproteáza
- poškození + úklid
  - apoptóza
  - pyroptóza
  - nekroptóza
  - zánětlivá reakce
  - proliferace

Inátní imunita
Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis
The ACCESS Randomized Trial

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Brunon Francois, MD
Steven P. Lecros, MD
Denis C. Anglès, MD, MPH
Jean-Paul Mira, MD, PhD
Xavier Witekole, MD
Thierry Heuguerer, MD
Dominique Perrotin, MD
Mark Tidwell, MD
Laurence Auberg, MD
Kenneth Kelln, MD
Jan Piri, MD
Takeo Tahashiba, MD
Fromv Perk, MD
Mart Blaise, DO
Chia-Sheung Chang, MD
Sandra Olvera, MD
Nasik Akawa, MD, PhD
Tatsuya Muroyama, MD, PhD
Roland Schein, MD
Andre C. Kalil, MD, MPH
Marc Van Nauffeln, MD
Melvin Lynn, PhD
Daniel P. Rosignol, PhD
Jagdish Gagani, PhD
Mary B. Roberts, MS
Janise L. Wheeler, BS, RN
Jean-Louis Vincent, MD, PhD

Importance Eritoran is a synthetic lipid A antagonist that blocks (poly)saccharide (LPS) binding to the cell surface MD2-TLR4 receptor. LPS is a major component of the outer membrane of gram-negative bacteria and is a potent activator of the innate inflammatory response.

Objective To determine if eritoran, a TLR4 antagonist, would significantly reduce sepsis-induced mortality.

Design, Setting, and Participants We performed a randomized, double-blind, placebo-controlled, multinational phase 2 trial in 197 intensive care units. Patients were enrolled from June 2006 to September 2010 and final follow-up was completed in September 2011.

Interventions Patients with severe sepsis (n=1061) were randomized and treated within 12 hours of onset of first organ dysfunction in a 2:1 ratio with a 6-day course of either eritoran trehalose (105 mg total) or placebo, with n=1394 and n=657 patients, respectively.

Main Outcome Measures The primary end point was 28-day all-cause mortality. The secondary end points were all-cause mortality at 3, 6, and 12 months after beginning treatment.

Results Baseline characteristics of the 2 study groups were similar. In the modified intent-to-treat analysis (randomized patients who received at least 1 dose) there was no significant difference in the primary end point of 28-day all-cause mortality with 28.1% (356/1204) in the eritoran group vs 26.9% (177/657) in the placebo group (P=0.59, hazard ratio, 1.05; 95% CI, 0.88-1.26; difference in mortality rate, 1.15% CI, –0.3 to 3.6); or in the secondary end point of 1-year all-cause mortality with 41.1% (290/657) in the eritoran group vs 43.3% (565/1204) in the placebo group, Kaplan-Meier analyses of time to death by year, P=0.79 (hazard ratio, 0.96; 0.83-1.13). No significant differences were observed in any of the prespecified subgroup analyses. Events, including secondary infection rates, did not differ between study groups.

Conclusions and Relevance Among patients with severe sepsis, the use of eritoran, compared with placebo, did not result in reduced 28-day mortality.

Trial Registration clinicaltrials.gov Identifier: NCT00334828

In summary, in this phase 3 trial eritoran did not significantly improve outcome for patients with severe sepsis and septic shock. Eritoran joins a long list of other experimental sepsis treatments that do not improve outcomes in clinical trials in these critically ill patients.

In summary, in this phase 3 trial eritoran did not significantly improve outcome for patients with severe sepsis and septic shock. Eritoran joins a long list of other experimental sepsis treatments that do not improve outcomes in clinical trials in these critically ill patients.

### Table 7: Other potential new treatment options to prevent or treat sepsis

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Developmental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific bacterial vaccines</td>
<td>Promotes antimicrobial clearance of common pathogens (Streptococcus spp., Staphylococcus spp., and Neisseria spp.)</td>
</tr>
<tr>
<td>Vaccine against bacterial lipopolysaccharide</td>
<td>Prevents endotoxin-mediated activation of the host immune response</td>
</tr>
<tr>
<td>Vaccines against staphylococcal or streptococcal superantigens</td>
<td>Attenuates superantigen-induced activation of CD4+ T lymphocytes and antigen-presenting cells</td>
</tr>
<tr>
<td>Recombinant glycans</td>
<td>Protein that decreases endothelial cell adherence, has immunomodulatory activity, and binds bacterial toxins</td>
</tr>
<tr>
<td>Polyoxymethylene columns, other blood purification strategies</td>
<td>Classes bacterial lipopolysaccharide, inflammatory cytokines, HMGCR, and other inflammatory mediators</td>
</tr>
<tr>
<td>Immunoabsorption strategies</td>
<td>Can induce inhibitory phenotype of macrophages and lymphocytes</td>
</tr>
<tr>
<td>Mitochondrial Slayer drugs</td>
<td>Improves cellular energetics and restricts apoptosis</td>
</tr>
<tr>
<td>Monoclonal antibodies to bacterial virulence factor and to common multiglycoprotein pathogens</td>
<td>Block bacterial virulence factors from invasive pathogens and promote immune clearance of pathogens</td>
</tr>
<tr>
<td>Anti-HMGCR monoclonal antibody</td>
<td>Prevents HMGCR-mediated inflammatory effects and endothelial barrier breakdown</td>
</tr>
<tr>
<td>Soluble TREM-1 mucin transcript 1</td>
<td>Blocks TREM-1 signalling on innate immune cells, restricting leucocyte activation in sepsis</td>
</tr>
<tr>
<td>Protein inhibition, monoclonal antibody to PCSK9</td>
<td>Blocks protein that cleaves small C-terminal domain of LDL receptor</td>
</tr>
</tbody>
</table>
| Neutrophilic formulations of intravenous immunoglobulins | IgG concentrates that have immune-modulatory effects, bacterial clearance, and 
C. difficile | Early clinical trials in pneumonia and sepsis |
| Promoting drugs | Lipoxysterase-derived lipidated mediators that promote resolution of inflammation, tissue repair, and clearance of damaged immune cells | Preclinical investigations |
| Low-dose corticosteroids | Anti-inflammatory effects and reduce the synthesis of acute phase proteins | Large phase 1 trials |
| β blockers for septic shock | Cardiovascular control and hemodynamic stabilization for myocardial protection | Phase 2 testing |
| orally administered probiotics | Prevention of pancreatic enzyme mediated gut epithelial injury, resulting in increased intestinal permeability | In phase 2 trials |
| Thymosin α 1 | Short peptide that is T-cell adjuvant and immune modulator for sepsis-induced immunosuppression | Phase 2 clinical trials |
| Mesenchymal stem cell therapy | Cells traffic to sites of injury and promote anti-inflammatory effects and tissue repair by paracrine secretion of soluble factors | Phase 2 testing in other indications; pilot studies in patients with acute respiratory distress syndrome and sepsis |

Sepse a inhibitory PCSK9?
Inhibitory PCSK9 (evolokumab, alirocumab)
SREBP zprostředkuje transkripci LDLR a PCSK9 ale

1. PCSK9 degraduje LDLR
2. zvýšení PCSK9 může limitovat statiny indukovaný vzestup LDLR
3. PCSK9 inhibitory tak mohou maximálně zvýšit LDLR a snížit LDL cholesterol
Targeting the Proprotein Convertase Subtilisin/Kexin Type 9 for the Treatment of Dyslipidemia and Atherosclerosis

Daniel Urban, MD, Janine Pöss, MD, Michael Böhm, MD, Ulrich Laufs, MD

Homburg/Saar, Germany

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Agent</th>
<th>Company/Sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>SAR236553/REGN727</td>
<td>Sanofi/Regeneron</td>
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<td>AMG 145</td>
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<td>RN316</td>
<td>Pfizer</td>
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<td></td>
<td>RG7652</td>
<td>Roche/Genentech</td>
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<td>LGT-209</td>
<td>Novartis</td>
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<td>Merck</td>
<td>Pre-clinical</td>
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<td>1B20</td>
<td>Merck</td>
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<tr>
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<td>J10, J16</td>
<td>Pfizer</td>
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<td>J17</td>
<td>Pfizer</td>
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<td>Mimetic peptides</td>
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<td>LDLR DNA construct</td>
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<td>Small-molecule inhibitors</td>
<td>SX-PCK9</td>
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<td>Antisense oligonucleotides</td>
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<td>RNA interference</td>
<td>ALN-PCS02</td>
<td>Alnylam</td>
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</tbody>
</table>
Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients
The GLAGOV Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helina Kassahun, MD; Jingyuan Yang, PhD; Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD, PhD; Jakub Podolec, MD, PhD; Antonius Oude Ophuis, MD, PhD; Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Danielle M. Brennan, MS; Steven E. Nissen, MD

The GLAGOV Randomized Clinical Trial
Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound

Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume

"In the GLAGOV study, we demonstrated that evolocumab has an effect on atherosclerosis, the underlying cause of cardiovascular disease. These FOURIER results show unequivocally the connection between lowering LDL cholesterol with evolocumab and cardiovascular risk reduction, even in a population already treated with optimised statin therapy," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen.
Genetické mutace PCSK9

PCSK9

LOF missense mutace

GOF nonsense mutace

 ldLR koncentrace

 LDL-C koncentrace

PCSK9 mutace mohou být homozygotní, nebo heterozygotní

GOF, gain of function; LOF, loss of function

PCSK9 mutace mohou být homozygotní, nebo heterozygotní

GOF, gain of function; LOF, loss of function

MINI-REVIEW

PCSK9 at the crossroad of cholesterol metabolism and immune function during infections

Francesco Paciullo¹  |  Francesca Fallarino²  |  Vanessa Bianconi¹  |  Massimo R. Mannarino¹  |  Amirhossein Sahebkar³  |  Matteo Pirro¹
Conclusion
Available evidence shows a strong association between PCSK9 levels and septic symptoms, which can be attributed to the cross talk between PCSK9 and liver LDLR. Overexpressed PCSK9 is found to decrease LPS clearance and increase inflammatory cytokines, while PCSK9 deficiency is shown to enhance LPS clearance and ameliorate sepsis-related inflammatory responses. Lack of efficient therapeutic approaches to modify inflammation in septic patients calls for new strategies to enhance clearance of pathogenic lipids and mitigate inflammatory responses.
Závěry
Od PAMPs a DAMPs k biomarkerům sepse

- PAMPs i DAMPs mohou být biomarkery
  - DNA/RNA patogenů, Heat Shock Protein...
- PAMPs a DAMPs jsou na počátku dráhy s řadou biomarkerů
  - od CD znaků přes interleukiny a chemokiny až k prokalcitoninu a reaktantům akutní fáze
- Biomarkery orgánových funkcí
  - troponiny, bilirubin, koagulační faktory...
- a také SOFA je kombinovaný biomarker!
- monitorování terapie zasahující vhodné dráhy?
Děkuji za pozornost