В ПОИСКАХ СВЕТА В КОНЦЕ ТУННЕЛЯ

БЕЛОБОРОДОВ В.Б.
ЗАВЕДУЮЩИЙ КАФЕДРОЙ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ РМАНПО
КОНФЛИКТА ИНТЕРЕСОВ НЕТ
IN MEMORIAM

1941 - 1997

Roger C. Bone, MD, Master TCCP,
ACCP Past President
1991 год

Сепсис = Инфекция + SIRS

Септический шок = Тяжелый сепсис + гипотензия

Тяжелый сепсис = Сепсис + СПОН

> 2 признаков:
○ 36 °C<T>38 °C  
○ ЧСС >90 /мин  
○ ЧД > 20 /мин (раCO2 <32 мм рт.ст.)  
○ 4000<Лейкоциты >12000/мкл (ПЯС > 10%)

SIRS
outcome sepsis shows that both pro- and anti-inflammatory cytokines
the pro-inflammatory phase is ascendant. Innate and adaptive immunity are sown relatively early while
clinical evidence that the seeds of the down-regulation of both
CARS (illustrated in Figure 1), there is experimental and
32 cytokine IL-6 and the anti-inflammatory cytokine IL-10
of death was marked elevation of
severe sepsis and the pattern associated with the highest risk
Cytokine levels were highest in those patients who died of
majority of the patients (82%) at presentation to the ED.
and 26% died, elevated cytokine levels were present in the
acquired pneumonia in whom 30% developed severe sepsis
cohort study of almost 2000 patients with community
human patients with sepsis as well. For instance, in a
Ojeda et al pro-inflammatory and anti-inflammatory markers. Andaluz-
state of sepsis could help identify patients who would benefit
from the hyper-inflammatory state to the anti-inflammatory
factors contribute to it? A marker or, more likely, a panel
patients with sepsis, but not SIRS
diminished and expression of its inhibitor was enhanced in
severe sepsis. Expression of nuclear factor-kB, a transcription
function to return to normal
during the immunosuppressive phase that allows immune
loss of cell-surface HLA-DR on circulating monocytes occurs
very early and that the transition to severe sepsis is
early and severe sepsis, enhanced expression of anti-
enhanced expression of pro-inflammatory cytokine genes in
both early and severe sepsis, enhanced expression of anti-
patients with sepsis, but not SIRS
levels of IL-6 and IL-8 (both of which can be considered pro-
Levels of IL-6 and IL-10 and MCP-1 (both of which
van der Poll and van Deventer
might be called the concurrent model (Figure 5) suggested by
Finally, the model usually ascribes survival to some event
inflammatory state are combined with markers of the
ratio of either biomarker alone.
not develop sepsis). In this study, plasma IL-10 was not
low (and probably not very different from patients who did
infection of some kind, he was treated with an anti-emetic and
a nearby medical center's ED. The pediatrician recommended that his mother take him to
waiting room and his temperature was still very elevated.
concerned because Rory had vomited in the pediatrician's
hospital. However, Rory's condition did not improve. On
the morning of Friday, March 30, Rory had a bout of
total nausea and vomiting, and his mother was worried.
Rory Staunton was a 12-year-old boy who grew up in
Queens in New York City. During gym class on Wednesday,
March 28, 2012, he dove for a basketball and scraped his arm.
Baron Jean-Louis Vincent is Professor of intensive care medicine at the Université libre de Bruxelles and intensivist in the Department of Intensive Care at Erasme University Hospital in Brussels.

Dr Vincent has signed more than 900 original articles, some 400 book chapters and review articles, and more than 1000 original abstracts, and has edited 102 books. He is co-editor of the "Textbook of Critical Care" (Elsevier Saunders, 7th Edition) and the “Encyclopedia of Intensive Care Medicine”
ТОЛЛ-ПОДОБНЫЕ РЕЦЕПТОРЫ И ПРОВОСПАЛАТЕЛЬНЫЕ ЦИТОКИНЫ
Сигналы патогенов — микробы

Сигналы поврежденных тканей

Иммунные клетки

Запуск сигналов

Запуск воспаления

Собственные медиаторы

Воспаление

PRR – рецепторы патогенов; TLRs – толл-подобные рецепторы; NOD-LRRs – белки с областью олигомеризации нуклеотидов насыщенной лейцином; RLHs – подобный геликазам ген I активирующийся ретинойной кислотой; ASC – апоптоетический белок содержащий домен активации и мобилизации.
ПРОВОСПАЛАТЕЛЬНЫЕ ЦИТОКИНЫ КАК МАРКЕРЫ ГИПЕРДИНАМИЧЕСКОЙ ФАЗЫ ВОСПАЛАНИЯ

Активация:
- Эндотелия
- Нейтрофилов
- Гепатоцитов
- Костного мозга

ИЛ8 > ИЛ6
МСР-1

Предикторы летальности
БИОМАРКЕРЫ АКТИВИРОВАННЫХ НЕЙТРОФИЛОВ И МОНОЦИТОВ ПРИ СЕПСИСЕ

- Чувствит. CD64 = PCT
- Специф. PCT > CD64
- Плотность экспрессии CD64 коррелировала с переходом сепсиса в тяжелый сепсис
- Низкая стабильность CD64 в крови с антикоагулянтами

Livaditi O et al. Cytokine 2006;36:283–90.


КОНЦЕНТРАЦИЯ ЛПС (НГ/Л) У ПАЦИЕНТОВ БЕЗ АБТ НА ДОГОСПИТАЛЬНОМ ЭТАПЕ

- После начала АБТ не наблюдалось повышения уровня ЛПС в крови
- Период полувывведения ЛПС после первого введения пенициллина = 90 минут

КОНЦЕНТРАЦИЯ ПРОВОСПАЛИТЕЛЬНЫХ ЦИТОКИНОВ (ПГ/Л) У БОЛЬНЫХ МИ (N=162)

Вывод:
Прогнозируемая неэффективность элиминации цитокинов из крови в снижении летальности

МУТАЦИЯ ЛЕЙДЕНА (МЛ) У БОЛЬНЫХ МЕНИНГОКОККОВОЙ ИНФЕКЦИЕЙ И ТЯЖЕЛЬМ СЕПСИСОМ ДРУГОЙ ЭТИОЛОГИИ

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<tr>
<th>Показатель</th>
<th>Менингококковая инфекция</th>
<th>Тяжелый сепсис другой этиологии</th>
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<tr>
<td></td>
<td>Всего</td>
<td>% МЛ</td>
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<tr>
<td>Всего</td>
<td>23</td>
<td>31</td>
</tr>
<tr>
<td>Выжило</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Умерло</td>
<td>5</td>
<td>60</td>
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Выводы:
- Диспропорциональное распределение пациентов с МЛ среди умерших и выживших
- Высокая вероятность тромбозов у умерших пациентов
- Прогнозируемая неэффективность активированного протеина С при наличии мутации Лейдена

Городнова ЕА и соавт. Клиническая анестезиология и реаниматология. 2006, 3 (1): 40-55.
<table>
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<tr>
<th>Показатель</th>
<th>Выжившие (204)</th>
<th>Погибшие (49)</th>
<th>p</th>
<th>Тенденция</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA</td>
<td>4 (2-6)</td>
<td>8 (5-11)</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>Lactate mmol/L</td>
<td>1.90 (1.30-2.98)</td>
<td>4.10 (2.30-7.70)</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>Systolic BP mmHg</td>
<td>100 (80-120)</td>
<td>82 (70-100)</td>
<td>0.001</td>
<td>↓</td>
</tr>
<tr>
<td>Glasgow</td>
<td>14 (13-15)</td>
<td>13 (12-14)</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>Ferritin ng/mL</td>
<td>339 (157-757)</td>
<td>1103 (385-2000)</td>
<td>0.000</td>
<td>↑</td>
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<tr>
<td>LDH UI/L</td>
<td>440 (332-670)</td>
<td>995 (608-2279)</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin μU/mL</td>
<td>12.3 (7.73-24.9)</td>
<td>8.4 (3.9-19.5)</td>
<td>0.003</td>
<td>↓</td>
</tr>
<tr>
<td>Transferrin mg/dL</td>
<td>164 (130-205)</td>
<td>119 (91-132)</td>
<td>0.000</td>
<td>↑</td>
</tr>
<tr>
<td>PCT ng/mL</td>
<td>1.07 (0.25-3.64)</td>
<td>3.86 (0.46-11.3)</td>
<td>0.032</td>
<td>↓</td>
</tr>
<tr>
<td>CRP μg/mL</td>
<td>17.2 (9.0-27.5)</td>
<td>18.6 (9.8-29.4)</td>
<td>0.687</td>
<td>↓</td>
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<tr>
<td>TNFα pg/mL</td>
<td>15.8 (10-27.4)</td>
<td>22.5 (11.8-49.1)</td>
<td>0.012</td>
<td>↓</td>
</tr>
<tr>
<td>IL-6 pg/mL</td>
<td>49.1 (23.1-13)</td>
<td>145 (49.3-422)</td>
<td>0.000</td>
<td>↓</td>
</tr>
</tbody>
</table>

СРАВНЕНИЕ КОЛИЧЕСТВА ФОЛЛИКУЛЯРНЫХ ДЕНДРИТНЫХ КЛЕТОК (CD21) И CD4 Τ-КЛЕТОК У ПАЦИЕНТОВ ТРАВМОЙ И СЕПСИСОМ

CD21

A

Травма

B

Сепсис

CD4

C

D

Hotchkiss RS, Karl IK, 2003
КОЛИЧЕСТВО ЛИМФОИДНЫХ ФОЛЛИКУЛОВ, СОДЕРЖАЩИХ В-КЛЕТКИ (CD20) В СЕЛЕЗЕНКЕ ПАЦИЕНТОВ ТРАВМОЙ И СЕПСИСОМ

травма

сепсис

Hotchkiss RS, Karl IK, 2003
The likelihood that the blood culture will be positive is unclear. The addition of other tests, especially PCR techniques, has helped detect the presence of pathogens in critically ill patients. PCR systems designed to detect the most frequently observed bacteria (and fungi) in patients with sepsis, as well as correlations of bacterial species with conventional blood culture, have approximately twice the number of positive samples compared with traditional tests.

In 2004, a large observational study showed that endotoxin was present in more than one-half of all patients admitted to intensive care units on the day of their admission, despite the fact that mice deficient in these proteins show enhanced survival in an experimental model of abdominal sepsis. These include real time multiplexed chemiluminescence to produce an oxidative burst response that is measured by the presence of SIRS symptoms. The presence of SIRS has been shown to increase such attempts when patients do not display localizing signs or infection. Approximately, 10% of the patients in this study developed severe sepsis, and the level of endotoxin was a predictor of the Sequential Organ Failure Assessment (SOFA) scores, and there is a consensus that HMGB1 levels do not offer any helpful prognostic information with regard to survival.

Despite the fact that mice deficient in these proteins show increased risk of nosocomial infection, there is a consensus that HMGB1 levels do not offer any helpful prognostic information with regard to survival. Sequential Organ Failure Assessment (SOFA) scores, and there is a consensus that HMGB1 levels do not offer any helpful prognostic information with regard to survival. However, there have been discrepancies in several reports correlating the results with other clinical data.

Another important category of DAMP is a group of S100 proteins, called calgranulins or myeloid related proteins, that are transmitted via co-stimulatory molecules, T-cell activation receptor, and the appropriate ''second signal'' is also correlated with monocyte HLA-DR expression. This approach has promise for detecting the presence of pathogens in critically ill patients. PCR systems designed to detect the most frequently observed bacteria (and fungi) in patients with sepsis, as well as correlations of bacterial species with conventional blood culture, have approximately twice the number of positive samples compared with traditional tests.

Blood cultures to detect bacteremia are the mainstay of diagnosis of sepsis. During the past decade, endotoxin, the classic PAMP, has been studied in patients with critical illness. There is significant evidence that patients with severe sepsis have defective adaptive immunity. These include real time multiplexed chemiluminescence to produce an oxidative burst response that is measured by the presence of SIRS symptoms. The presence of SIRS has been shown to increase such attempts when patients do not display localizing signs or infection. Approximately, 10% of the patients in this study developed severe sepsis, and the level of endotoxin was a predictor of the Sequential Organ Failure Assessment (SOFA) scores, and there is a consensus that HMGB1 levels do not offer any helpful prognostic information with regard to survival. However, there have been discrepancies in several reports correlating the results with other clinical data.

Bone recognized the importance of CARS, which follows the hyper-inflammatory state in septic patients, more than 15 years ago. Recently, several biomarkers of the immunosuppressive phase have been studied in patients with critical illness, as well as correlations of bacterial species with conventional blood culture, have approximately twice the number of positive samples compared with traditional tests.

There is significant evidence that patients with severe sepsis have defective adaptive immunity. Macrophages (or monocytes) may display peptides derived from phagocytized protein. Class II major histocompatibility complex (MHC) proteins, B7 on the antigen-presenting cell. Instead of providing co-stimulation to T-cells. If recognized by the T-cell's unique antigen receptor, and the appropriate ''second signal'' is also correlated with monocyte HLA-DR expression. This approach has promise for detecting the presence of pathogens in critically ill patients. PCR systems designed to detect the most frequently observed bacteria (and fungi) in patients with sepsis, as well as correlations of bacterial species with conventional blood culture, have approximately twice the number of positive samples compared with traditional tests.

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ОСОБЕННОСТИ СОСТОЯНИЯ ИММУННОЙ СИСТЕМЫ

Механизмы саморегуляции:
- Иммунная толерантность
- Контроль нежелательных иммунных реакций
- Контроль избыточных иммунных реакций

Обеспечиваются сетью контрольных пунктов
- Комплекс мембранных рецепторов и их лигандов, действующих как иммуномодуляторы
- Супрессирующих или активирующих ключевые сигнальные пути и модулирующие эффекторные функции клеток
- Описано более 20 иммунорегуляторных путей
НАИБОЛЕЕ ИЗУЧЕННЫЕ ИММУНОРЕГУЛЯТОРНЫЕ ПУТИ ПРИ СЕПСИСЕ

- PD-1/PD-L1/ PD-L2
- TIM-3/Galectin-9
- CTLA-4 и LAG-3 [25]

При активации клеток эти рецепторы появляются на поверхности, обеспечивая очень высокий уровень активности (включая секрецию множества цитокинов)

Их количество снижается после фазы активации, после разрешения острого повреждения, что приводит к восстановлению тканей и заживлению ран, формирование иммунной памяти

Иммунная регуляция с помощью контрольных пунктов (CR) и их лигандов (CR–L), эффект блокады контрольных пунктов нейтрализующими антителами. Рецепторы контрольных пунктов регулируют величину, масштабы и распространённость иммунного ответа, баланс стимулирующих и подавляющих сигналов для иммунных клеток со стороны антигенпредставляющих и целевых клеток.

Блокада иммунных контрольных пунктов рецепторов и их лигандов нейтрализующими антителами (Anti-CR Ab и Anti-CR–L Ab) снижают воспалительный ответ и восстанавливают иммунную дисфункцию.

Высокая экспрессия подавляющих рецепторов контрольных пунктов супрессирующих иммунные реакции и блокирование контрольных пунктов восстанавливает здоровое состояние. Баланс гомеостаза между антимикробным иммунитетом и аутоиммунными реакциями поддерживается в физиологическом состоянии (a). При продолжительной стимуляции, подавляющие контрольные пункты гиперэкспрессированы, что ограничивает неконтролируемый ответ и иммунные повреждения, но одновременно супрессирует эффективность противомикробного ответа (b). Блокирование ингибиторных пунктов контроля может подавлять эти гиперингибирующие сигналы, восстанавливая нормальное иммунное состояние (c).

opportunistic infections long term, indicating that immunosuppression and immune impairments are maintained over time. Immunosuppression rather than hyper-immunity drives the response to sepsis, as also supported by the evidence that clinical trials focussed on reducing hyper-immunity/SIRS have provided conflicting and disappointing results.

Negative immune checkpoints (including PD-1, PD-L1, TIM-3, CTLA-4, LAG-3 and others) play a causal role in this persistent immunosuppression. Their expression on both innate and adaptive immune cells is greatly increased in septic patients, correlating with loss of immune functions (including innate antibacterial activities from monocytes, macrophages or neutrophils and T-cell production of cytokines and cytotoxic factors), immune cell apoptosis, reduced pathogen clearance and increased patient mortality. Most of these immune dysfunctions can be at least partially restored by blocking checkpoint pathways (Figs. 1b, 2c). This strategy is currently being investigated in several preclinical and clinical ex vivo studies with promising results in septic patients, suggesting that host-targeted immunotherapy may rescue suppressed antimicrobial immunity, reduce susceptibility to infection and improve patient survival.

Immune checkpoints and checkpoint blockade in ALD

Many features of sepsis and septic shock resemble those observed in ALD patients who acquire bacterial infection. This is particularly pertinent in the context of severe ALD, including decompensated cirrhosis, alcohol-related liver failure, alcohol-related acute-on-chronic liver failure (ACLF) and SAH. Furthermore, in abstinent patients immune defects persist over a long term, a common feature with sepsis survivors. Hence, there may be a strong parallelism between mechanisms of immune dysfunction in sepsis and those at play in ALD. As discussed, several studies have investigated the contribution of negative immune checkpoints to the immunopathophysiology of sepsis and several pre-clinical and clinical studies are defining the parameters of immune checkpoint blockade as a therapeutic strategy in these patients. However, no such clinical investigations exist in the context of ALD, highlighting a large gap in the possibility to develop new host-targeted strategies for ALD and its complications, for which there are no current specific treatment options.

In a 2015 study, we performed an in-depth ex vivo immunological characterisation of antibacterial responses in ARC and SAH patients and we were the first group to show that immune dysfunctions observed in SAH patients relate directly to increased expression of PD-1 and TIM-3. Immune alterations were directly correlated with severity of disease, and gut-derived bacterial products were driving these immune dysfunctions, therefore highlighting a parallel with bacterial sepsis.

Fig. 3

Immune checkpoints as therapeutic targets. Monoclonal antibodies currently in clinical development or tested in clinical trials against CTLA-4, PD-1, PD-L1, LAG-3 and TIM-3, as new anticancer agents, as these same immune checkpoint antibodies also represent the most promising therapeutic agents for future clinical trials in ALD.