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25 YEARS Current Opinion in Immunology

Monitoring the immune response in sepsis: a rational approach to administration of immunoadjuvant therapies

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Preliminary studies suggest that a subgroup of septic patients with severe immune alterations is at high risk of death or nosocomial infection and therefore could benefit from adjunctive immune stimulating therapies. There is thus an urgent need for robust biomarkers usable in routine conditions evaluating rapidly evolving immune status in patients. Although functional testing remains a gold standard, its standardization remains challenging. Therefore, surrogate markers such as monocyte HLA-DR expression, are being developed. Such biomarkers of immune functionality will enable a novel approach in the design of clinical trials evaluating immunostimulating therapies in sepsis at the right time and in the right patient.

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Current Opinion in Immunology 2013, **25**:477–483

This review comes from a themed issue on **Host pathogens**

Edited by **Marc Pellegrini** and **Bruce D Walker**

For a complete overview see the Issue and the Editorial

Available online 28th May 2013

0952-7915/$ – see front matter,

http://dx.doi.org/10.1016/j.coi.2013.05.006

Introduction

Sepsis has been called a hidden public disaster. In 2012, over 20 million patients world-wide are estimated to be afflicted by sepsis annually and recent epidemiological analyses showed that mortality from severe sepsis and septic shock is still elevated — around 30% both in Europe and USA [1]. Both pro and anti-inflammatory responses are initially induced in septic shock patients with the secondary occurrence of sepsis-induced immunosuppression [2••]. Importantly, the intensity and duration of sepsis-induced immune alterations have been associated with increased risk of deleterious events in patients, while over 70% of total mortality after septic shock occurs in a delayed fashion (i.e. after the first three days). This constitutes the rational for the initiation of innovative clinical trials testing adjunctive immunostimulating drugs in sepsis [2••].

However, as there is no clinical sign of immunosuppression, there is an urgent need for rapid, sensitive and specific biomarkers of the robustness of patients' immune status. This ability to semi-quantitate patient immune status will contribute to the success of future immune targeted clinical trials based on the inclusion of appropriately stratified patients. The review will focus on recent advances in aspects of immunomonitoring in septic patients with the perspective of a use as stratification tools in immunostimulating clinical trials.

The concept of sepsis-induced immunosuppression

Several lines of clinical evidence suggest that septic patients who survive the initial few days of the disorder acquired various defects in immunity. This is mainly illustrated by their decreased capacity to overcome initial or secondary infectious challenges. Indeed, a recent post-mortem study showed that approximately 80% septic patients had unresolved septic foci at time of death [3•]. Similarly, many pathogens responsible for nosocomial sepsis in intensive care unit [ICU] (*Acinetobacter*, *Candida*, etc.) are weakly virulent opportunistic germs usually isolated from severely immunodepressed patients [4]. This is consistent with the high incidence in septic patients of reactivation of latent viruses (cytomegalovirus, herpes simplex virus) that are normally held in abeyance by host immunity [5–7]. Finally, clinical studies showed a link between altered immune functions and patients' susceptibility to secondary infections [8•,9•,10,11]. This phenomenon of ICU-acquired immune dysfunctions has been called compensatory anti-inflammatory response syndrome, sepsis-induced immunosuppression, or cellular reprogramming [2••,12].

Although not exhaustively described, pathophysiologic mechanisms at play have begun to be understood (Table 1). In particular, epigenetic regulation, energetic failure, central and endocrine regulations, increased apoptosis or endotoxin tolerance have been shown to be playing a role both in clinical observations and animal models of sepsis [13–16].

Table 1

Sepsis-induced immune dysfunctions: pathophysiology at a glance

Mechanisms	Features of sepsis-induced immune alterations
Endotoxin tolerance	↓ pro-inflammatory ↑ anti-inflammatory cytokine production ↓ Ag presentation capacity
Apoptosis	↓ cell number Cell anergy
Energetic failure	Cell anergy Apoptosis Mitochondrial dysfunction
Anti-inflammatory mediators	↓ activating co-receptor expressions ↑ inhibitory co-receptor expressions Cell anergy Endotoxin tolerance
Epigenetic regulation	↓ pro-inflammatory gene expressions Cellular reprogramming
Central and endocrine Regulations	↓ pro-inflammatory cytokine production

Such immune alterations affect both the innate and adaptive parts of the immune response, occur rapidly after patients' admission, and are present both peripherally in circulating blood cells but also locally in organs [17••]. They thus represent a very profound and systemic process. Importantly, a number of clinical observations showed that the intensity and duration of these sepsis-induced immune dysfunctions (evaluated by different approaches [18]) are associated with increased risk for deleterious outcomes (death or secondary ICU-acquired infections).

Monitoring innate immune alterations in sepsis and related therapies

Innate immune cells represent the first line of defence after an infection and thus play a central role in the control of pathogens and initiation of adaptive immune responses.

Animal models of sepsis and experimental studies in patients depicted altered innate immune cell functions [13]. However, except for monocytes, few studies identified a link between these alterations and clinical outcomes in patients. In particular, recent studies showed that, after sepsis, circulating neutrophils have altered functions such as impaired bacterial clearance, abnormal radical oxygen species production, and decreased recruitment to infected tissues [19,20]. Similarly, recent experimental studies proposed a role for late onset myeloid-derived suppressor cells (MDSC) in sepsis pathophysiology [21,22]. However, to date, no clinical studies showed a link between these parameters and clinical outcomes in patients. Regarding MDSC, it might be due to the complexity of their immunophenotyping and to the absence of any consensually accepted phenotype in humans. Interestingly, recent studies described NK cell functional alterations (reduced IFNγ secretion) and decreased cell number in sepsis [23–25]. However clinical studies formally identifying a link between these alterations and clinical outcomes are still lacking. Moreover, the transfer of such functional approaches (*in vitro* cytokine release [26,27] or granulomatous response [25]) in clinical practice remains very complex.

Dendritic cells (DC), the professional antigen presenting cells, are sentinels in tissues and play an important role in initiation and modulation of T cell responses. DCs in sepsis exhibited altered phenotype and functions with, in particular, a decreased expression of Human Leukocyte Antigen-DR (HLA-DR) and reduced secretion of pro-inflammatory cytokines upon stimulation by bacterial products [11,28]. Interestingly, in septic patients, the peripheral DC count is low and this decrease has been shown to be associated with worsened clinical outcomes in sepsis including death and nosocomial infections [11,29].

Besides the previously mentioned clinical studies, many studies have described altered monocyte phenotype and functions in sepsis [30–32]. In particular, decreased expression of HLA-DR (mHLA-DR) on circulating monocytes has been observed and is proposed as a surrogate marker of immune failure [33•]. Increased circulating IL-10 production has been postulated to play a role in this process and studies showed the association between increased plasmatic IL-10 concentration and clinical outcomes such as nosocomial infections [34,35]. mHLA-DR downregulation has been shown to be predictive of complications in numerous clinical conditions (Table 2) and is applicable for clinical practice with standardized tests [36,37]. Importantly, studies show an association between the lack of recovery of mHLA-DR expression overtime and secondary infections in sepsis [9•,10]. This finding highlights the importance of the timing of immunomonitoring in regard to the expected homeostatic response and the phase of sepsis. In other words, immune enhancing therapy needs to be applied during the immunosuppressive phase of the disorder as indicated by decreased mHLA-DR expression. Therapeutic protocols with GM-CSF, G-CSF and IFNγ have been conducted in sepsis with the aims to stimulate innate immune function, improve myelopoiesis and limit lymphocyte apoptosis. Small clinical studies in ICU patients with sepsis or trauma showed no effect to decrease mortality but there was a beneficial effect on illness severity and rate of pathogen clearance [38,39••,40–42]. Interestingly, no study detected any adverse events. The lack of overall benefit on mortality in these pilot studies might be related to the failure to select patients based upon their respective immune status, for example, using monocyte mHLA-DR expression. In those clinical studies in which mHLA-DR was measured, immune-adjuvant therapy