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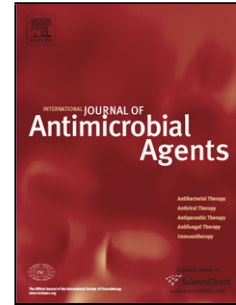
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What is the pathophysiology of the septic host upon admission?

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Abstract

The enormous case–fatality rate of severe sepsis and septic shock has resulted in considerable efforts being made towards understanding their complex mechanisms of pathogenesis. This has been done with the hope that agents that interfere with the pathways of pathogenesis and modulate the immune response of the host may be candidates for therapy. Disappointing results from most trials of immunomodulators in sepsis have led to understanding that the progression of patients to multiple organ dysfunction syndrome involves blunting of the pro-inflammatory cytokine storm. Instead, the compensatory anti-inflammatory response syndrome (CARS) develops, which is characterized by immunoparalysis. Components of this syndrome are impaired phagocytosis by neutrophils, decreased expression of HLA-DR on monocytes, impairment of ex vivo cytokine stimulation of monocytes, CD4 lymphopenia due to apoptosis of lymphocytes and predominance of anti-inflammatory T_h2 and regulatory T-cell responses over pro-inflammatory T_h1 and T₁₇ responses. CARS is not the sole explanation for the failure of trials of immunomodulators in sepsis. Recent data from the Hellenic Sepsis Study Group demonstrate that components of CARS upon transition from sepsis to severe sepsis/shock differ in relation to the underlying type of infection. These data underscore that the pathogenesis of sepsis presents considerable heterogeneity from one patient to another. That heterogeneity should be taken into consideration when deciding to administer an immunomodulator.

Keywords:

Sepsis

Pathogenesis

Immunity

Cytokines

Immunoparalysis

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1. Introduction

Severe sepsis and septic shock are among the leading causes of death worldwide, the threat they pose being aggravated by their multidimensional pathogenesis.

Sepsis may arise as the result of an infectious process supervening in an otherwise healthy individual. It may also happen in the event of an infection arising in a vulnerable host. This type of host may have a chronic illness such as heart failure, obstructive pulmonary disease, renal failure, diabetes mellitus type 2, solid tumour or haematological malignancy. As a consequence, even if such a patient survives, his quality of life may be severely impaired [1]. This signifies that sepsis is both the end result and the common denominator for death in a variety of very common illnesses. It is estimated that every year almost 1.5 million new cases of severe sepsis and/or septic shock develop in North America and another 1.5 million new cases in Europe. Data from the Hellenic Sepsis Study Group demonstrate that the case–fatality rate from severe sepsis is 33% and from septic shock >50% [2]. This enormous case–fatality rate creates the necessity for novel approaches to treatment [3]. Such novel approaches comprise a vast array of agents aimed at modulating the immune response of the septic host. However, the wide application of such agents necessitates both in-depth knowledge of the pathogenesis of sepsis and an ability to recognize how the host immune system functions when clinical signs of sepsis appear.

Our broad understanding of the complex molecular pathways leading to activation of the immune response and the subsequent development of sepsis often creates the impression that clear answers to both questions are available. However, the failure of most clinical trials of immunomodulators in sepsis indicates that we are far from

understanding how the immune system functions when clinical sepsis appears [4]. The present review attempts to provide a systematic approach to both questions.

2. Overview of the pathogenesis of sepsis

2.1. Stimulation of the innate immune response

It is believed that sepsis arises in the host due to the systemic activation of the immune system after stimulation by an invading microorganism. These microorganisms reside in an infectious focus. They bear common, well-conserved structures known as pathogen-associated molecular patterns (PAMPs). Examples of PAMPs are muramyl dipeptide (MDP) of the cell wall of Gram-positive cocci, lipopolysaccharide (LPS) of the outer membrane of Gram-negative bacteria, the outer lipid envelope of influenza A type viruses, bacterial CpG DNA and fungal β -D-glucan. PAMPs bind to and activate receptors on immune cells, mainly blood monocytes and tissue macrophages, known as pattern recognition receptors (PRRs). These are located either in cell membranes or the cytoplasm. Well-defined PRRs are Toll-like receptors (TLRs), triggering receptors expressed on myeloid cells (TREMs), dectin-1 and the inflammasomes [5].

TLR2 and TLR4 are transmembrane receptors that bind peptidoglycan and LPS, respectively. TLR3 and TLR9 are located in the cell cytoplasm and bind viral lipid envelope RNA and bacterial CpG DNA, respectively. TREM-1 is a transmembrane receptor of blood neutrophils and blood monocytes; its ligand is currently unknown. The β -D-glucan of the fungal cell membrane binds to dectin-1. Once PRRs are activated by their ligand, a series of intracellular adaptor molecules is activated, ending in the activation of several transcription factors, of which nuclear factor kappa B (NF κ B) and activator protein 1 (AP-1) are the most important. These factors

prime the transcription of a variety of pro-inflammatory and anti-inflammatory cytokines. Examples of pro-inflammatory cytokines are tumour necrosis factor-alpha (TNF- α), interleukin (IL)-1 β , IL-6 and IL-8. The major anti-inflammatory mediators are IL-10 and soluble cytokine receptors such as TNFR1 (known as p55), TNFR2 (known as p75), IL1RA and TREM-1. Pro-inflammatory cytokines orchestrate clinical pro-inflammatory phenomena like fever, tachycardia, leukocytosis, exudation from vessels, hypotension, and secretion of acute phase proteins. Neutrophils recruited to the inflammatory site release oxygen radicals, leading to tissue destruction. Anti-inflammatory cytokines compensate for the pro-inflammatory effect of pro-inflammatory cytokines [6–8].

The inflammasomes are recently described multimers of proteins located in the cell cytoplasm. Three types of inflammasome have been described: NALP, IPAF and nucleotide-binding oligomerization domain (NOD). Twelve NALP inflammasomes have been described, each consisting of a pyrin domain, a NACHT domain, a NAD domain and a leucine-rich repeat (LRR) domain. NALP3 is also known as cryopyrin. Two IPAF inflammasomes have been recognized, each consisting of a caspase recruitment domain (CARD), a NACHT domain and an LRR domain. The six recognized NOD inflammasomes each consist of a CARD domain, a NACHT domain, a NAD domain and an LRR domain. Certain ligands, like bacterial MDP and viral nucleic acids, bind to LRRs. This leads to the formation of multimeric complexes and to the activation of pro-caspase 1 to caspase 1. The latter cleaves pro-IL-1 β to the mature IL-1 β [9, 10].

PRRs may also be activated by endogenous host products released from tissues during the inflammatory process. Examples are mitochondrial DNA from muscle tissue, crystals of uric acid formed after DNA degradation, oxygen radicals released

from neutrophils and high-mobility group box 1 (HMGB1) protein, a non-histone DNA-bound protein released after cell death. These endogenous products are known as danger-associated molecular patterns (DAMPs or alarmins). Mitochondrial DNA binds to TLR9 [11], whereas crystals of uric acid, oxygen radicals and HMGB1 activate the inflammasomes [10,12]. It has recently been described that activation of the NALP3 inflammasome by crystals of monosodium urate is synergistic with activation of TLR4 by LPS, leading to excess production of IL-1 β [13].

2.2. Stimulation of the adaptive immune response

An antigen that stimulates the innate immune response is presented to naive CD4 lymphocytes by HLA-DR cell surface receptors of the major histocompatibility complex class II. The lymphocytes then differentiate into four subtypes defined by the type of secreted cytokine and its function. Differentiation is primed by a complex of heterodimer cytokines known as the IL-12/IL-23 complex. The four cell subtypes and their functions are: 1) T_h1 lymphocytes that secrete TNF- α , IL-2 and interferon-gamma (IFN- γ) and propagate pro-inflammatory responses; 2) T_h2 lymphocytes that secrete IL-4, IL-6 and IL-10 and mediate anti-inflammatory responses; 3) regulatory T cells (T_{reg}) that mediate anti-inflammatory responses by either cytokine secretion or direct cell cytotoxicity [14] and 4) T₁₇ lymphocytes that secrete IL-17 and mediate chemotaxis and priming of the function of neutrophils at the infection site [15].

2.3. Onset of immunoparalysis

The initial stimulation of the innate immune system by a pathogen leads to over-production of pro-inflammatory cytokines, a cytokine storm, which mediates the onset of the systemic inflammatory response syndrome (SIRS). There is a profound need for the host to counterbalance the exaggerated inflammatory response and a

systemic anti-inflammatory response is generated with the following characteristics:

1) predominance of T_{h2} and T_{reg} responses over T_{h1} and T_{17} responses; 2) CD4 lymphopenia and hypofunction of B lymphocytes; 3) failure of blood monocytes to produce adequate amounts of cytokines when stimulated *ex vivo* by bacterial ligands; 4) decreased expression of HLA-DR on monocytes; and 5) impaired phagocytosis by neutrophils.

This response is known as the compensatory anti-inflammatory response syndrome (CARS), which leads to generalized impairment of the immune function of the host, known as immunoparalysis [16]. Apoptosis of lymphocytes is another mechanism contributing to the development of CARS [17].

It seems that neutrophils play a crucial role during the phase of immunoparalysis. More precisely, neutrophils are characterized by high mobility, which allows them to adhere easily to the vascular endothelium, roll between tightly bound endothelial cells and migrate to the infected tissues. Upon progression of sepsis the neutrophil cytoskeleton loses its flexibility, leading to entrapment of the cells in the infected tissues. It is known that neutrophils over-produce oxygen radicals, which mediate tissue injury, a process that is facilitated upon entrapment [18]. As a consequence, during CARS, circulating neutrophils and neutrophils infiltrating tissues behave in different ways. The former have impaired function, whereas the latter mediate tissue injury. Furthermore, tissue neutrophils constitute a reservoir for the anti-inflammatory IL-10, thus contributing further to sepsis-induced immunoparalysis [19].

It is believed that during CARS the host is susceptible to two further complications – the development of multiple organ dysfunction syndrome (MODS) and secondary bacterial infections [20]. A simplified representation of the pathogenesis of sepsis is shown in Fig. 1.

[Fig. 1 here]

3. The problem of patient heterogeneity

Based on the scheme for the pathogenesis of sepsis described in Fig. 1., clinical trials with immunomodulators targeting specific molecules in that cascade should have been successful. Instead most of these trials ended with disappointing results, creating questions about the reasons for failure [4]. Two explanations may be given for these disappointing results: 1) many of the immunomodulators that are active during the pro-inflammatory phase of sepsis have been administered in patients with CARS and 2) the current theory of pathogenesis is based on the assumption that every septic patient behaves in a similar way. However, factors such as the underlying type of infection and the causative pathogen may create considerable heterogeneity among patients.

Although many authors support the first explanation [16, 20], little evidence exists for or against the second explanation. In an attempt to resolve this, the Hellenic Sepsis Study Group studied the early status of the innate and adaptive immune responses among a large number of septic patients [21]. Blood samples were prospectively collected from 505 patients within 24 h of the clinical presentation of sepsis. Samples were transferred within 8 h to a central laboratory and immunophenotyping was done. Patients were divided into five categories according to the type of underlying infection: acute pyelonephritis (183 patients); community-acquired pneumonia (97 patients); acute intra-abdominal infection (100 patients); primary bacteraemia (61 patients) and ventilator-associated pneumonia or hospital-acquired pneumonia (VAP/HAP, 64 patients). The pathogens isolated for every infection except community-acquired pneumonia were mostly Gram-negative bacteria. In every

infection category comparisons were made between patients with sepsis and patients with severe sepsis/shock.

The status of early innate immunity was assessed by: 1) the expression of HLA-DR on monocytes; 2) the rate of apoptosis of monocytes; 3) the absolute counts of natural killer (NK) cells and NKT cells; and 4) the rate of apoptosis of NK cells and NKT cells. Results revealed that, contrary to expectation, considerable differences exist upon progression from sepsis to severe sepsis/shock in relation to the type of underlying infection (Table 1).

[Table 1 here]

The status of early adaptive immunity was assessed by 1) the absolute counts of CD4, CD8 and CD19 lymphocytes; and 2) the rate of apoptosis of CD4 and CD8 lymphocytes. Similar differences to those seen for innate immunity were observed in relation to the type of underlying infection (Table 1).

Among the types of infection studied, VAP (the most common cause of sepsis among patients hospitalized in an intensive care unit) presents unique characteristics regarding the innate and adaptive immune responses of the patients. Blood was sampled from 36 patients with VAP and sepsis and compared with samples from 32 patients with sepsis due to other types of infection. Both groups of patients were well-matched for disease severity and co-morbid illnesses. Results revealed that the state of immunoparalysis was considerably greater among patients with VAP than among patients with other types of infections as evidenced by 1) lower absolute counts of CD4 lymphocytes; 2) greater rate of apoptosis of monocytes; and 3) impaired ex vivo cytokine stimulation of monocytes. Moreover, patients with VAP could be divided into two groups depending on ex vivo cytokine stimulation of

monocytes – those patients with adequate stimulation and those patients with defective stimulation. Survival of the former was prolonged compared with the latter [22]. Based on results from in vitro stimulation of peripheral blood mononuclear cells of healthy volunteers with isolates from patients with VAP, it may be hypothesized that it is the progressive increase of bacterial inoculum in the bronchial tree that leads to VAP and primes the status of immunosuppression of the host.

4. Conclusions

There is no doubt that our current understanding of the pathogenesis of sepsis has been considerably broadened over the last decade. However, since the disappointing results of clinical trials of immunomodulators, this knowledge seems to be only theoretically valuable. We should admit that although the development of sepsis follows a similar path in every patient, this path is different from one patient to another for various reasons, one of the most important being the underlying type of infection. This should be taken into thorough consideration for the successful clinical development and application of immunomodulators.

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Competing interests: None.

Ethical approval: Not needed.

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[Figure legend]

Fig. 1. Simplified representation of the pathogenesis of sepsis.

CARS, compensatory anti-inflammatory response syndrome; HMGB1, high-mobility group box 1; LPS, lipopolysaccharide; MDP, muramyl dipeptide; MODS, multiple organ dysfunction syndrome; mtDNA, mitochondrial DNA; NKs, natural killer cells; ↓, decrease of function; T_h, helper T cells; T_{reg}, regulatory T cells.

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Table 1

Early changes of innate and adaptive immunity in a cohort of 505 Greek patients during transition from sepsis to severe sepsis/shock in relation to the underlying type of infection (modified by [21])

	Acute pyelonephritis	CAP	IAI	Primary bacteraemia	VAP/HAP
Innate immunity					
HLA-DR expression on monocytes	↓	-	↓	-	-
Monocyte apoptosis	↓	-	-	-	-
NK cell count	-	↓	-	-	-
NK cell apoptosis	-	-	-	-	↑
NKT cell count	-	-	-	-	-
NKT cell apoptosis	↓	-	-	↑	↑
Adaptive immunity					
CD4 lymphocyte count	-	↓	↓	-	-
CD4 lymphocyte apoptosis	-	-	-	-	-
CD8 lymphocyte count	-	↓	↓	-	-
CD8 lymphocyte apoptosis	-		↓	-	-

B lymphocyte count	-	↓	-	-	-
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CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infections; NK, natural killer; VAP, ventilator-associated pneumonia; ↑, increase; ↓, decrease; -, stable.

