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Cellular processes in sepsis

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Summary

Sepsis, the systemic inflammatory response to an infection, is an increasingly common condition. It represents a major healthcare problem as affected patients have a high morbidity and mortality leading to high direct and indirect costs. This article describes the progression from a simple infection to septic shock and multi-organ failure, with a special emphasis on the body's response at the cellular level.

Pathogen recognition by the host is followed by a cascade of pro- and anti-inflammatory mediators that attempt to defend the body and prevent further harm. Both pathogen virulence and host resistance regulate the severity of the inflammatory response. As a result of the inflammatory insult, mitochondria are damaged functionally and structurally. Since mitochondria are responsible for intracellular energy production, mitochondrial dysfunction places the cells at risk of developing energy failure and, consequently, cell death. However, sepsis is characterised by a lack of tissue necrosis and the ability of most – if not all – organs to recover completely. This underlines the assumption that organ dysfunction during sepsis is predominantly a functional problem which appears to relate to the creation of a new balance between energy generation and expenditure. Hence, organ dysfunction could be viewed as a protective mechanism for the patient and may represent a state analogous to hibernation, which can be reversed once the infection is overcome and inflammation has abated. More research is needed to develop better directed and timed therapeutic interventions that can reduce the high morbidity and mortality of this common condition.

Key words: sepsis; inflammation; mitochondrial dysfunction; organ failure; suspended animation

Introduction

Sepsis, severe sepsis and septic shock represent increasingly grave stages of the systemic inflammatory response to severe infection. Such patients have a high mortality, considerable long-term morbidity and they spend a prolonged time in both the intensive care unit and hospital, leading to high direct and indirect costs [1]. Reported mortality rates of 40–60% have not changed significantly in the past 20 years despite intense research and recent advances in treatment, although the case mix has altered considerably with increasing numbers of elderly and/or immunosuppressed patients now being treated [2–4]. A recent study from 454 German intensive care units revealed a

Glossary

ATP	adenosine triphosphate
CD	cluster of differentiation
cGMP	cyclic guanosine monophosphate
DNA	deoxyribonucleic acid
IL	interleukin
IRAK	interleukin-1 receptor-associated kinase
LPS	lipopolysaccaride (endotoxin)
MyD	myeloid differentiation protein
NOD	nucleotide oligomerization domain
NRF	nuclear respiration factor
PPARg	peroxisome proliferator-activated receptor gamma
RNA	ribonucleic acid
TAK	TRAF-associated kinase
Tfam	transcription factor A
TIR	toll/interleukin-1 receptor homologous region
TLR	toll-like receptor
TNF	tumour necrosis factor
TRAF	tumour necrosis factor receptor-associated factor

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sepsis prevalence of 23% [5]. The intensive care unit and hospital mortality rates of patients with severe sepsis (including septic shock) were 48% and 55%, respectively.

This article describes cellular mechanisms underlying sepsis. We highlight the progression from a simple infection to septic shock and multi-organ failure, with special emphasis on the body's response at the cellular level and with the hypothesis that organ 'failure' may represent a protective mechanism.

Innate immunity and the inflammatory response to infection

Bacteria and man live, and have always lived, in a very close, symbiotic relationship. A considerable number of bacteria exist on the surfaces of every human being, predominantly in the digestive tract. Not surprisingly, the skin and gut mucosa are the most important barriers for preventing bacterial invasion of the human host. However, when this barrier fails or is artificially disrupted (eg by burns, catheters, surgical wounds), the host becomes susceptible to pathogen invasion. The second line defence is the immune system that can recognise, fight and destroy invading germs. Although highly effective, the immune system is not perfect. Both a lack of immune reaction to a pathogen or an overwhelming immune response will severely endanger the host. The first situation makes the organism susceptible to infections; the latter may well destroy the pathogen but may also severely damage the host.

Sepsis represents a systemic response of the immune system to an infection. Both pathogen virulence and host resistance regulate the severity of the inflammatory response. The virulence of the pathogen depends on the type, number and site of invading organisms. The resistance and immunocompetence of the host are determined by multiple factors including age, gender [3], genetic predisposition [6–9], nutritional status, medications, drug/alcohol abuse, and underlying conditions such as cancer or diabetes [4].

The cellular components of the innate immune system

The innate (= inborn) immune system consists of humoral and cellular components. The humoral component contains cytokines, chemical substances that are directly toxic to invading microbes or that act as mediators for other cells. The cellular component include circulating monocytes, tissue macrophages, neutrophils and lymphocytes [10].

Tissue macrophages, which are derived from blood monocytes, are capable of engulfing and digesting microbes. They can also recruit other phagocytes by secreting cytokines. Macrophages present particles of dispatched microbes (= antigens) to lymphocytes and hence interact closely with the adaptive (= cognitive) immune system.

Polynuclear cells include neutrophil, eosinophil and basophil granulocytes. Neutrophils are important phagocytes, but can also destroy invading pathogens by secreting toxic substances such as reactive oxygen species [11]. Attracted by chemokines, neutrophils migrate and translocate into the infected tissue where they fight the pathogens [12]. The total blood neutrophil count may initially drop significantly during acute infection. In response, neutrophils are increasingly liberated from the stimulated bone marrow, leading to a subsequent increase in the total neutrophil count (leukocytosis). In addition, more immature forms of neutrophils are released from the bone marrow, which can be differentiated using light microscopy (leftward shift of the neutrophils). Eosinophil and basophil granulocytes are responsible for secreting inflammatory mediators and thereby creating an inflammatory milieu. This leads to dilation and leakage of the adjacent vessels, facilitating the migration of inflammatory cells into the infected tissue and leading to efflux of plasma. As a consequence of these processes, clinical signs of local inflammation occur, including redness (rubor), swelling (tumor), increased temperature (calor) and pain (dolor).

Importantly, cells of the innate immune system can fight invading pathogens directly without involvement of the adaptive immune system although very close interactions exist with B and T lymphocytes [13]. There are also important relationships with the coagulation system [14, 15] and with other tissues such as blood vessels [16], adipose tissue [17] and the gut [18]. Therefore, no definitive answer can be given to the question as to where, precisely, innate immunity begins and ends [19].

The humoral components of the innate immune system

Cytokines are the humoral components of the innate immune system and act either directly on invading pathogens, or as mediators between cells and organs. Reactive oxygen species in high concentrations have a toxic effect on bacteria by damaging their cell walls. In lower concentrations, these molecules are important regulatory mediators [11]. Interleukins (IL) and tumor necrosis factor (TNF) are other mediators that have the ability to promote inflammation from a localised to a systemic process. Some of these cytokines are stored in myeloid cells and are rapidly secreted after contact with microbes. In addition, the production of these cytokines is stimulated by complex mechanisms in a time dependent manner. In the following sections, some modes of activations will be described. However, it is important to realise that the presented schemata are markedly simplified and not yet fully elucidated.

Pathogen recognition and activation of the inflammatory cascade

Cells of the innate immune system can detect typical molecular patterns of most, if not all, microbes, including viruses, bacteria, fungi and protozoa. Examples of such patterns are lipopolysaccharides (LPS, endotoxin) from the cell wall of Gram-negative bacteria, lipoteichoic acid and peptidoglycan from Gram-positive bacteria, unmethylated bacterial DNA, or double-stranded viral RNA. These non-mammalian molecules are recognised by three families of specific pattern recognition receptors: Toll-like receptors (TLR), intracellular NOD proteins, and peptidoglycan recognition proteins [10, 19]. To date ten different types of TLR have been identified in humans [20, 21]. Most act in conjunction with other molecules such as CD14, or with other TLRs expressed on the cell surface. Binding of a microbial molecule to its specific TLR results in signal transmission by Toll/interleukin-1 receptor homologous region (TIR) adaptor proteins to a complex intracellular cascade of enzymes [22]. These enzymes consist of kinases, enzymes that phosphorylate and thus activate proteins. In the case of Gram-negative bacteria, LPS from the bacterial wall binds to TLR4 and CD14, activating the TIR domain called myeloid differentiation protein (MyD)-88 (fig. 1).

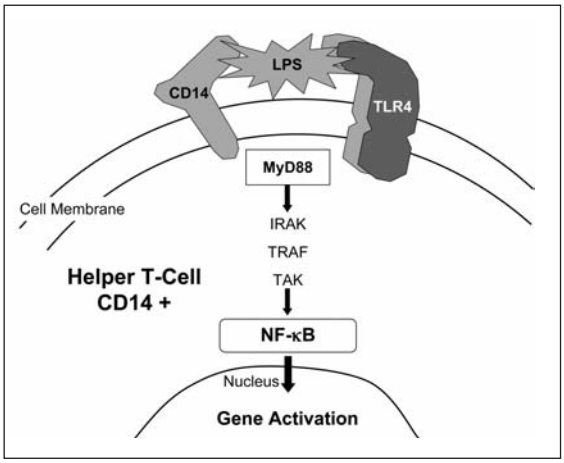

Figure 1

Lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, is recognised by TLR4 and CD14 on the surface of immune cells. This activates an intracellular cascade, which results in the activation of NFkB dependent genes (see text for details). It is important to realise that the presented schema is markedly simplified, and not fully elucidated.

This activates the interleukin-1 receptor-associated kinase (IRAK) which, in turn, stimulates the tumour necrosis factor receptor-associated factor (TRAF) and, consequently, the TRAF-associated kinase (TAK) [10]. As a result, the nuclear transcription factor, nuclear factor kappa B (NFkB) is liberated from its inhibitor (IkB) and hence is able to dislocate into the cell nucleus. The actions of NFkB include binding to DNA, thereby activating hundreds of specific genes coding for proteins which are increased during the inflammatory process [23]. Although the most studied, NFkB is only one example of many transcription factors, that are activated during sepsis in a time-dependent manner [24].

One of the genes expressed via NFkB codes for TNF, which further amplifies local NFkB activation. On a systemic level, TNF carries the inflammation to other organs and, with interleukin (IL)-6, induces the production of acute phase proteins in the liver, for example, C-reactive protein and fibrinogen. TNF also plays a very important role in the activation of programmed cell death or apoptosis. Another activated enzyme of major importance is inducible nitric oxide synthase (iNOS). Its concentration increases after gene activation, and its function is to generate high levels of nitric oxide (NO), a fundamental pro-inflammatory molecule [25]. NO activates other enzymes such as guanylyl cyclase, which leads to the production of cyclic guanosine monophosphate (cGMP). The clinical effects of these processes include local and systemic vasodilation, which, if severe, can lead to hypotension and shock. Interestingly, pharmacological inhibition of both the inducible and constitutive isoforms of the NOS enzyme increased the blood pressure of patients with septic shock, but had a detrimental effect on overall survival [26–30]. This led to the assumption that NO may also have beneficial effects that are important factors in patient survival and that total blockade of NO production or its downstream effects is inadvisable.

Anti-inflammatory activity during sepsis

During sepsis, pro-inflammatory mechanisms are heavily activated. However, anti-inflammatory mechanisms are activated at the same time [31]. These include secretion of specific cytokines such as IL-10 and the soluble TNF receptor and a decrease in the lymphocyte cell count [32]. The overall balance is pro-inflammatory in the early phase of sepsis and anti-inflammatory later on [33]. The advantage of this systemic anti-inflammatory response may be the attenuation of deleterious systemic pro-inflammatory effects and the concentration and compartmentalisation of the inflammation at the site of infection [10]. However, when anti-inflammatory mechanisms dominate, the immune system is depressed (immunoparesis), thus increasing the body's susceptibility to nosocomial infections and the reactivation of dormant pathogens such as cytomegalovirus [34, 35]. Patients with severe sepsis might therefore benefit from immune system stimulation [36]. However, more clinical studies are needed to confirm this new concept and better bedside tools are needed to confirm timing and need for such an intervention.

Microcirculation and mitochondrial dysfunction

Early sepsis is characterised by vasodilation and intravascular volume depletion (from increased capillary leak and external losses) leading to underfilling of the heart and a low cardiac output. This is compounded by myocardial depression and potentially causes an oxygen supply-demand imbalance in various organ beds [37]. Fluid administration during early sepsis increases oxygen delivery to the organs and improves clinical outcome [38]. However, efforts to enhance oxygen delivery by fluid and dobutamine administration during established sepsis with concurrent organ failure show no benefit and may be potentially harmful [39, 40]. This suggests an evolution of the septic process and underlines the importance of optimal timing of interventions.

Alterations of the microcirculation are also well documented in septic patients [41] and these may decrease oxygen delivery to the tissues. Within the cells, mitochondria require oxygen in order to produce adenosine triphosphate (ATP) by the process of oxidative phosphorylation. This utilizes more than 90% of total oxygen consumed by the body and is responsible for most of the ATP generated by most cell types within the body, with the neutrophil being a particular exception. ATP is the predominant source of intracellular energy and is needed for all energy utilizing cellular functions. Mitochondria are structurally and functionally damaged by the inflammatory insult following infection [42, 43]. Three separate mechanisms appear to cause sepsis induced mitochondrial dysfunction. Direct inhibition of the respiratory enzyme complexes can result from increased concentrations of nitric oxide and its metabolite, peroxynitrite. There may also be direct damage from increased production of reactive oxygen species. Recent studies also report genetic down regulation of new mitochondrial protein formation [12]. This damage is facilitated by intra-mitochondrial defence mechanisms (reduced glutathione, superoxide dismutase) being overwhelmed [44].

Mitochondria are repaired or regenerated by the process of mitochondrial biogenesis. This is stimulated by increased expression of nuclear transcription factors such as Tfam and NRF-1 [45, 46]. Clearly, this may prove to be a useful strategy for accelerating organ recovery, so approaches that will stimulate biogenesis may play an important role. NO itself is a stimulator of mitochondrial biogenesis [47].

Suspended animation

Insufficient oxygen supply due to macro- and microcirculatory failure will cause tissue hypoxia, while impaired oxygen utilisation due to mitochondrial dysfunction will lead to tissue dysoxia. Both mechanisms decrease intracellular ATP production. This may not only impair organ specific cell functioning, but may also result in a loss of cell integrity, as maintenance of cellular structure is energy-dependent. Hence, severe lack of ATP will lead to cell dysfunction and, eventually, cell death. One might therefore assume that organ dysfunction is a consequence of extensive cell death in the affected tissues and organs. However, post mortem studies revealed little, if any, evidence of cell death within dysfunctional/failed organs during sepsis [48, 49]. Of note, therapeutic options blocking apoptosis in lymphocytes were beneficial in preclinical studies, but this has not yet been tested in patients [50]. The lack of tissue necrosis has led to the hypothesis that organ dysfunction might be more of a functional than structural phenomenon and thus potentially reversible.

The cell may switch its use of ATP only to processes essential for cell survival, such as maintenance of its membrane potential. By shutting down energy-dependent organ-specific functions the cell can decrease its total ATP expenditure, allowing the net ATP balance to remain positive despite a decrease in ATP production. This "suspended animation" is analogous to aestivation and hibernation [51, 52]. Although this is a new concept for multi-organ dysfunction in sepsis, it is a well-established protective strategy in a variety of animals as an adaptive response to heat, cold or drought, and it is a recognised phenomenon within cardiomyocytes during ischaemic heart disease and persisting hypoperfusion [53]. Hence, organ dysfunction during sepsis could be possibly viewed as an adaptive and potentially protective process that will help to prevent cell death. Once infection is overcome and more natural conditions resume, mitochondrial function is restored. ATP production then increases and the cell can regain its normal metabolism and organ-specific functions [33, 54].

Sepsis is a multi-system disorder

Sepsis and its associated multi-organ dysfunction syndrome can be viewed as a vigorous response of the host's innate immune system to a pathogen. However, it is increasingly clear that this process involves the interaction of the immune system with mitochondrial, endocrine, and metabolic pathways. The response to a septic insult is dynamic with distinct differences between the acute and chronic phases of the illness. After an initial wave of pro-inflammatory activity, a predominantly anti-inflammatory phase follows. The initial changes are coupled with increased endocrine, thermogenic and metabolic activity, excessive catabolism and fuel utilisation. The later anti-inflammatory phase is associated with declining levels of numerous hormones, bioenergetic failure and a reduced metabolic rate. If the host can successfully clear the infection, the resolution of both pro- and anti-inflammatory responses will be activated. Evidence suggests that this stage is also highly regulated, though much more research is needed to better understand underlying mechanisms. Interestingly, most organs have the ability to recover completely. This underlines the assumption that organ dysfunction during sepsis is not a structural problem but predominantly functional and potentially reversible [55, 56].

Future perspectives

Although numerous mechanisms have been elucidated in recent years, many important questions remain to be answered. These include the timing and intensity of activation of both pro- and anti-inflammatory molecules and cells and their complex interplay with different cells and tissues. The importance of the host's genetic background, age and underlying health status must be emphasized. There is hope for the future that specific and timed therapeutic interventions can reduce the high morbidity and mortality of patients with sepsis, though there is an urgent need for bedside biomarkers to guide these treatments.

Conclusion

Sepsis arises if an infection progresses into a systemic inflammatory disease. The organism will respond to an infectious stimulus with immune system activation, including both cellular and humoral components. An initial recognition of the pathogen is followed by a cascade of pro- and anti-inflammatory mediators that attempt to defend the body and prevent further harm. Pathogens are able to cause mitochondrial dysfunction by causing either inhibition or damage to the mitochondria or by having a depressant effect on its genome. Organ dysfunction perhaps represents a protective mechanism for the patient, leading to a state of hibernation, which is reversed once the infection is overcome. Septic mitochondrial damage and energy failure appears to be the major stimulus for mitochondrial protein turnover, a process called biogenesis. More research is needed to develop specific and timed therapeutic interventions that can reduce this high morbidity and mortality condition.

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