LEADING ARTICLE

The Role of Mediators in Sepsis Resolution

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Biological mechanisms associated with the induction of sepsis have been well characterized. In contrast, events and mediators associated with the resolution of sepsis and inflammation are less well understood. Sepsis may resolve due to the down-regulation of the factors that initiate it, although this is an unproven hypothesis. Alternatively, sepsis resolution may be mediated by signaling pathways that are distinct from those that initiate the process. Among mediators known to be involved in sepsis, there is evidence that failure of serum tumor necrosis factor-α, and possibly interleukin-6 (IL-6), levels to fall during the course of sepsis are associated with development of multiple organ failure and non-survival. The role of other factors in sepsis resolution, such as the counter-regulatory cytokines IL-10 and transforming growth factor-β, the central regulator nuclear factor-κB, and the role of clearance of infection, are not well characterized.

Treated sepsis associated with severe infection follows one of four broad clinical paths [1]:

- early death with failure to achieve hemodynamic stabilization
- hemodynamic stabilization followed by rapid recovery
- hemodynamic stabilization followed by prolonged multiple organ failure (MOF) with gradual recovery
- hemodynamic stabilization followed by prolonged and ultimately fatal MOF.

A substantial proportion of patients with sepsis get better, presumably as a consequence of appropriate antibiotic therapy, source control (if there is a localized site of infection), and transient physiological support of failed organ systems. What are the biological events that mediate this process? Can a better understanding of this process lead to novel therapeutic targets or strategies? What is the difference between those who recover and those who develop fixed MOF and succumb?

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A great deal is known about how infection induces a septic response, and how this septic response damages the host. Critical events in the triggering of sepsis are likely to include [2]:

- activation of pattern recognition receptors of the innate system
- nuclear translocation of nuclear factor-κB (NF-κB)
- induction of NF-κB-dependent effector genes, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), chemokines, and adhesion molecules.

In contrast, less is known about the mechanisms, events, and mediators that lead to the resolution of sepsis.

If it is assumed that sepsis is an exaggerated and, on balance, detrimental process, then the treatments that we lack at the bedside are those that can switch off this established sepsis process. In theory, resolution might occur because of the neutralization or cessation of production of mediators that initiate the process. Alternatively, and not mutually exclusively, separate signaling pathways may be responsible for mediating the resolution of an established septic episode.

Interestingly, most of the pharmacological antagonists of mediators that contribute to the initiation of sepsis are

only effective in animal models of sepsis when administered prior to the application of a septic insult [3]. Moreover, when these agents have been evaluated in clinical trials, after sepsis is established, they have proven either ineffective or detrimental [4]. There are multiple pharmacokinetic, pharmacodynamic, and epidemiological reasons that might explain the failure of these therapies. However, one possible explanation is that mediators such as TNF-α and IL-1β, whilst critical to the initiation of sepsis, are not involved by virtue of their disappearance in the resolution of sepsis. Recently, an effective adjuvant therapy for severe sepsis has been developed — drotrecogin alfa (activated), a recombinant human Activated Protein C [5]. However, the precise mechanism of the beneficial action of this agent is not known — a fact exemplified by the potential protean actions of the compound [6]. Whilst it can be presumed that this agent enhances the resolution of sepsis, the mechanisms of this beneficial action remain speculative.

It is increasingly recognized that the biology associated with resolution of inflammation has not been well characterized [7]. The purpose of this article is to review the role of known mediators of sepsis in the resolution phase of the illness.

What switches sepsis on?

The role of mediators in the resolution phase can only be considered after a brief discussion of their role in the initiation of sepsis. The first step in the induction of sepsis is the activation of phylogenetically conserved receptors that recognize invasion of the host by pathogenic microorganisms. This process is undertaken by receptors that recognize molecular structures, termed pathogen-associated molecular patterns (PAMPs), that are shared by many pathogens, but not expressed by hosts (Table 1) [2].

These receptors trigger intracellular signaling pathways that lead to activation of NF-κB (Fig. 1) and other transcriptional regulators that, in turn, lead to the transcription of a large number of genes involved in inflammation. Some of these are also regulators of inflammation, such as TNF-α and IL-1β, which may serve to spread inflammatory activation to distal sites and provide positive-feedback amplification of inflammatory responses. Other genes are involved in down-regulation and these may function in the fine-tuning of inflammatory responses, such as IL-10 and transforming growth factor-β (TGF-β). Many of the other induced genes are responsible, either directly or indirectly, for the generation of effector responses, including nitric oxide (NO) production, the expression of adhesion molecules, the production of chemokines, chemotaxis, and inflammatory cell activation. It is widely believed that the actions of these effector molecules contribute to tissue damage and organ failure during sepsis. Many of these factors are also highly effective at killing and/or containing invading microorganisms.

Table 1. The microbial origins of PAMPS and their recognition by host receptors.

PAMP	Microbial origin	Host receptor
LPS	Gram-negative cell wall component	TLR4/CD14 NOD1/2 TREM-1 Macrophage scavenger Receptor β2 integrins
Lipotechoic acid	Gram-positive cell wall component	TLR2
Mannan	Fungal cell wall	Mannose binding protein Mannose receptor
CpG DNA motif	Unmethylated prokaryotic DNA pattern	TLR9
Peptidoglycan	Bacterial cell wall component	TLR2 PGRP family
Zymosan	Fungi	TLR2/TLR6
N-formyl peptides	*N*-formylmethionine of bacterial proteins	F-met receptor 1 F-met receptor 2
Lipoproteins	Bacterial pattern amino-terminal tripalmitoylated cysteine	TLR2
Unknown	Neisserial surface component	TLR1/TLR2
Flagellin	Motile bacteria	TLR5
Double-stranded RNA	Viral RNA	TLR3

F-met: formylmethionine; LPS: lipopolysaccharide; PAMPs: pathogen-associated molecular patterns; PGRP: peptidoglycan recognition protein; TLR: Toll-like receptor; TREM: triggering receptors expressed by myeloid cells.

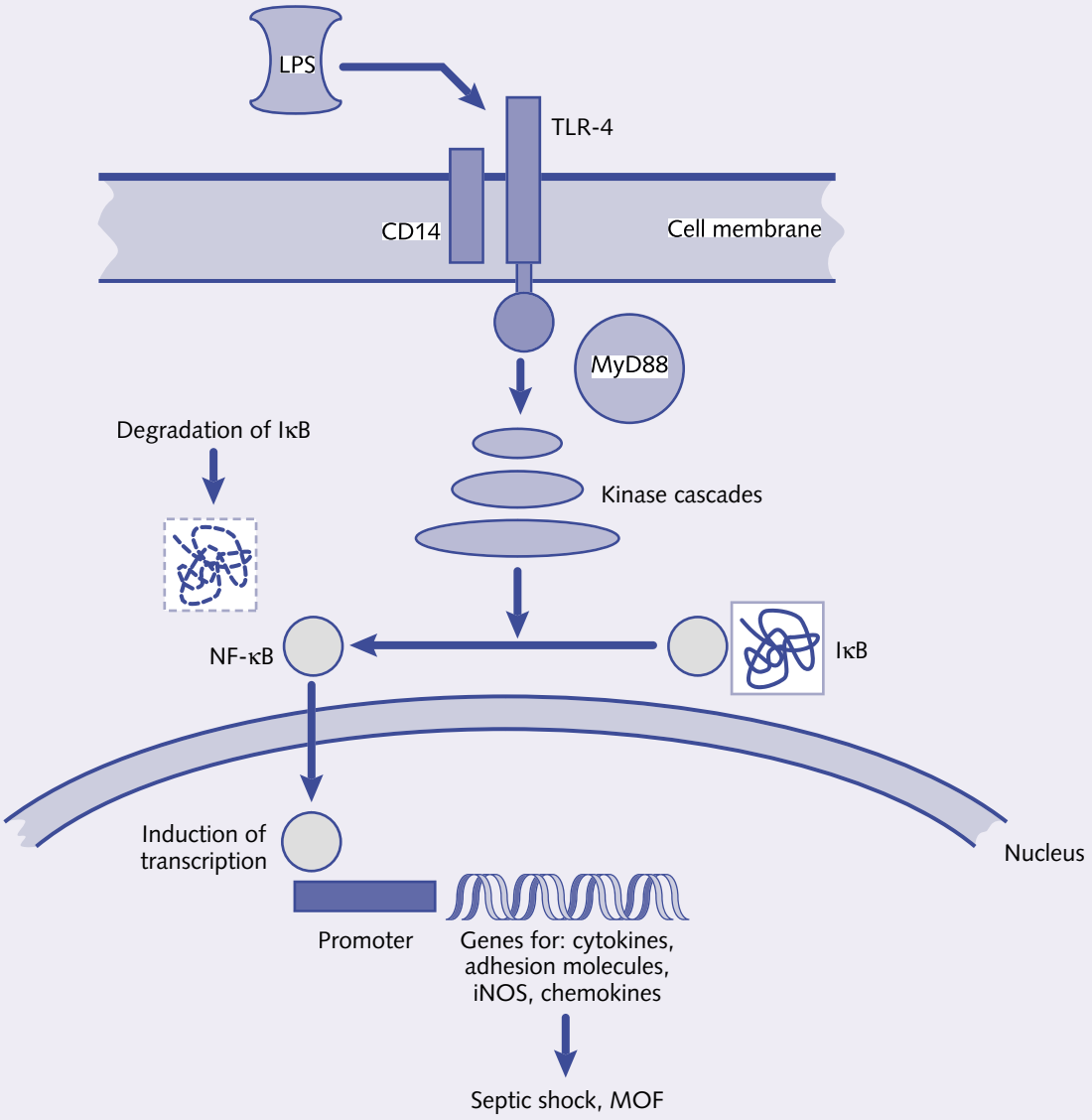
Factors that may produce persistent sepsis

The process that initiates sepsis is (by definition) infection, usually bacterial or fungal. In critically ill patients with sepsis, it seems reasonable to presume that factors that prevent resolution of sepsis and result in prolonged MOF might include the following, which are by no means mutually exclusive.

Persistence of the primary infective process

Infective processes differ in how easily they can be controlled. Some infective processes are amenable to rapid clearance (e.g. meningococcal disease with

Figure 1. LPS recognition by TLR4 stimulates NF-κB nuclear translocation, leading to septic shock.



IκB: inhibitor of NF-κB; iNOS: inducible nitric oxide synthase; LPS: lipopolysaccharide; MOF: multiple organ failure; MyD88: myloid differentiation factor 88; NF-κB: nuclear factor-κB; TLR: Toll-like receptor.

antibiotics, infected and obstructed urinary tract with drainage and antibiotics). In contrast, other infective processes are difficult to control and their persistence may be responsible for the continuance of sepsis and MOF (e.g. fecal peritonitis, mediastinitis, *Staphylococcus aureus* pneumonia with multiple lung abscesses).

Translocation of intestinal bacteria and/or bacterial product across the gut wall

This process, which is induced by gut damage associated with shock, might represent a potential explanation for the ongoing presence of PAMPs, resulting in sepsis and MOF, even after the primary process has been controlled. This is speculative, especially as there is evidence to show that although selective digestive decontamination is effective at reducing bacterial translocation in animals, this is not associated with amelioration or prevention of MOF in experimental animals or patients [8,9].

Acquisition of nosocomial infections in the intensive care unit

Many patients with severe sepsis develop secondary infections arising as a consequence of defects in local defense mechanisms associated with intensive care unit

(ICU) therapies (e.g. intubation), and/or immunoparesis induced as a consequence of sepsis [10]. The presence of these infections may lead to continued exposure of the host to PAMPs and, therefore, the persistence of sepsis and MOF, even after the primary process has been controlled.

Sepsis with MOF is an auto-inflammatory process

Although triggered by infection, sepsis with MOF continues in the absence of PAMPs. Persisting sepsis results in tissue damage and MOF, despite control and clearance of the initiating infection [11,12].

Role of mediators in the persistence or resolution of sepsis

The relative contribution of these factors, described above, to the persistence of sepsis and MOF, and thus delay in resolution, is neither known nor understood in terms of the molecules that mediate these alternative processes. However, the activities of various mediators that might contribute to persistence versus resolution of sepsis have been studied in patients and animal models of sepsis.

TNF-α, IL-1β, and their endogenous antagonists

TNF-α and IL-1β are critical mediators in the induction of sepsis. Does sepsis resolve simply when TNF-α and IL-1β levels fall sufficiently? It is often stated that these central mediators are only transiently elevated in sepsis [13,14]. This observation is based on animal studies of bolus endotoxemia, and is advanced as an explanation for the weak relationship between the admission level of these mediators in patients and survival, their absence in some patients with sepsis, and the failure of therapies that antagonize their action to improve outcome [13,14]. This hypothesis would also explain why anti-TNF-α and anti-IL-1β therapies are only effective in animal models when administered prior to application of the septic insult [3]. Despite this, there is evidence that a decreased level of TNF-α is associated with sepsis resolution. It is likely that failure to detect TNF-α and IL-1β in some patients with sepsis is due to the use of insensitive assays and the inclusion of patients with mild sepsis (which might be in the process of resolving). Several studies have reported serial TNF-α levels in a large number of septic shock patients, which are likely to represent a 'sicker' population. These studies consistently report elevated levels of TNF-α and, critically, early death or development of prolonged fatal MOF is associated with persistent elevation of mean TNF-α concentrations [1,15–18]. However, a similar relationship has not been established for IL-1β [15,18]. These data would suggest that among septic shock patients, persistent elevation of TNF-α, but not IL-1β, is associated with the development of MOF.

Soluble TNF receptors (TNFRs; p55 and p75), which bind and neutralize TNF-α, and an endogenous IL-1β receptor antagonist (IL-1ra), are released into the serum of patients with sepsis [19]. Thus, it is possible that these anti-inflammatory mediators may play a role in determining the resolution of sepsis and MOF. If these factors do play a role in sepsis offset, rising levels should be associated with improved outcome. Elevated levels of these mediators are found in patients with sepsis and septic shock, with admission levels of TNFR [19,20] and IL-1ra [21] positively correlated with outcome. In terms of temporal patterns, rising levels of mean serum TNFR at day 10 were actually associated with subsequent death [19]. The strongest evidence that these mediators do not mediate resolution of sepsis is their failure to improve outcome when administered exogenously [4]. Although the anti-inflammatory action of these mediators might lead to the prediction that they contribute to sepsis resolution, neither the temporal pattern, nor the experimental data, support this.

IL-6

IL-6 is the serum cytokine for which levels at admission are most closely correlated with death [14]. IL-6 levels generally fall quite rapidly after admission, even in patients with ongoing sepsis and MOF. However, three randomized, controlled trials enrolling patients with sepsis or acute respiratory distress syndrome have shown that therapeutic intervention was associated with a more rapid fall in serum IL-6 levels compared with control patients [5,22,23]. In two of these trials (drotrecogin alfa [activated] and lung protective ventilatory strategy), but not in the third (anti-TNF-α monoclonal antibody), this greater fall in IL-6 levels was associated with a therapy that improved outcome. This raises the possibility that declines in IL-6 levels may be associated with sepsis resolution. However, there is mixed evidence to support this hypothesis from studies that have measured serial IL-6 levels in patients with sepsis and septic shock. These studies report that IL-6 levels fall in the first 24–48 h after admission in all patients. Similar declines were observed in survivors and non-survivors [1,24], although one study reported persistent elevation of IL-6 among non-survivors at day 10 and day 13 [20]. The role of IL-6 in sepsis resolution is uncertain, although most evidence points towards more rapid declines in serum IL-6 being associated with sepsis resolution and improved outcome.

IL-10 and TGF-β

IL-10 and TGF-β are important counter-regulatory anti-inflammatory cytokines in sepsis and, thus, represent prime candidates as factors that mediate sepsis resolution [25]. However, this potential role is clouded by their involvement in the induction of a state of relative immunoparesis, which may predispose patients to nosocomial infections leading to prolonged MOF [25]. Increased levels of serum IL-10 are found in the circulation of most, but not all, patients with sepsis, and levels at the time of admission correlate with both the outcome and the concentrations of pro-inflammatory cytokines. No studies have measured serial IL-10 levels in large cohorts of sepsis patients, although a study that measured IL-10 levels in four patients with septic shock for 5 days, showed that IL-10 levels peaked during the first 48 h, but remained detectable for 3–5 days after admission [26]. Animal data derived using treatment with recombinant IL-10 and anti-IL-10 monoclonal antibodies suggest that IL-10 can play a role in sepsis resolution, although the timing of administration is critical [25].

The concentrations of serum TGF-β in patients with sepsis may be low or normal compared with healthy controls [27]. Mice with deletions of the TGF-β1 gene develop spontaneous organ failure associated with infiltration of mononuclear cells, which indicates that this gene may play a role in controlling inflammatory responses [28]. It is not known whether induction of TGF-β expression occurs during sepsis resolution. It seems likely that both these mediators play a role in sepsis resolution, although it remains possible that they 'fine tune' inflammatory responses rather than switch them off. Their potential role in inducing relative immunoparesis complicates assessment of their role in sepsis resolution.

NF-κB

NF-κB is a family of highly phylogenetically conserved transcriptional regulators that serve to integrate the cellular response to a variety of stimuli, including infection, and play a critical role in the development of sepsis [2,21,29–33]. Mammalian members of the NF-κB family are homo- or heterodimers of five NF-κB subunits: RelA (p65), c-Rel, RelB, p50, and p52. The pathogen-mediated activation of the nuclear translocation of NF-κB involves the phosphorylation- and ubiquitination-mediated proteolysis of a family of NF-κB inhibitors, known as IκB proteins. These proteins, which include IκBα, IκBβ, and IκBϵ, bind different components of the NF-κB complex in the cytoplasm, and prevent the translocation of NF-κB dimers into the nucleus where they are active [34]. Additionally, IκBα appears to be involved in the export of active NF-κB out of the nucleus [35]. Regeneration of IκB proteins is likely to play a role in switching off NF-κB mediated responses, and it is of note that NF-κB stimulates the expression of IκBα as part of a presumed negative-feedback loop [34]. Mouse knock-out studies reinforce the importance of this mediator: the deficiency of components of the NF-κB system produce an increased susceptibility to infection, and excessive activation resulting in multiorgan inflammation [36–38]. The central role of NF-κB (expressed in many cell types, activated by PAMPs and pro-inflammatory cytokines, and acting to induce expression of multiple effector genes) raises the possibility that sepsis persists as long as nuclear translocation of NF-κB continues, and that sepsis resolves in conjunction with NF-κB inactivation.

Pathogen clearance in sepsis resolution

Although systemic inflammatory responses can be induced by factors other than infection, sepsis is, by definition, induced by infection [39]. The discovery of pattern-recognition receptors of the innate immune response, especially the Toll-like receptor family, which function as key activators of inflammatory responses, reinforces the importance of infection in the induction of sepsis. However, it is not known if systemic innate immune responses are down-regulated only when infection is cleared or contained. Current theories of the pathogenesis of sepsis emphasize the role of host factors in determining the severity and duration of sepsis [11,12]. Nevertheless, appropriate antimicrobial therapy and source control clearly improves the outcome of sepsis and, presumably, enhances sepsis resolution [40,41]. However, experimental evaluation of this possibility is limited by difficulties associated with measuring the eradication of infection. This is largely due to the insensitivity of microbiological culture methods, especially in the presence of concomitant antimicrobial therapy, and the inability of imaging techniques to distinguish sterile from infected collections [42].

Conclusion

Much of the investigation of the pathogenesis of sepsis has focused on the initiation phase of sepsis. This has led to an increasingly sophisticated understanding of the complex events associated with the development of sepsis. This review argues that biological events associated with sepsis resolution are poorly characterized, but may be of substantial relevance. The relative paucity of data concerning the levels of mediators during the resolution stage of sepsis makes it difficult to draw definitive

conclusions about the role of many mediators in sepsis resolution. Nevertheless, the persistent presence of TNF-α, and possibly IL-6, appears to portend ongoing MOF and a poor outcome. New studies are needed to follow the level of pro- and anti-inflammatory mediators during the resolution phase of sepsis. Such studies should look to identify reductions in pro-inflammatory mediator levels or induction of anti-inflammatory mediators that occur in conjunction with resolution of organ failure. Although such observed changes may be part of a causal pathway, this should not be assumed. It is also possible that different signaling pathways are involved in switching sepsis off than those that initiate it. In particular, the temporal pattern of NF-κB nuclear translocation is worthy of study, together with mediators that might contribute to the down-regulation of NF-κB nuclear translocation.

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