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Recent advances in the pathophysiology and molecular basis of sepsis-associated organ dysfunction: Novel therapeutic implications and challenges

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ABSTRACT

Sepsis is one of the most common reasons for critically ill patients to be admitted to an intensive care unit and, despite advances in overall medical care, it represents a major clinical problem and remains the leading cause of death in the critically ill patient population. Although sepsis has been defined as a systemic inflammatory syndrome, in which there is an identifiable focus of infection, clinical trials aimed at anti-inflammatory therapeutic approaches have largely failed to identify an effective therapeutic target to improve clinical outcomes in sepsis. Very recently, the third international consensus definitions have been advocated for sepsis and septic shock. Thus, sepsis is now defined as life-threatening organ dysfunction due to a dysregulated host response to infection. A better understanding of the molecular mechanisms involved in the pathogenesis of sepsis and its resultant organ failure has been sought, and the development of therapies targeted at preventing or limiting molecular events associated with the progress of fatal organ failure, hence leading to improvement of outcomes, is urgently needed. This review article provides an overview of possible pathogenic mechanisms underlying the development of multiple organ dysfunction in sepsis and discusses pharmacological agents regarded as promising in treatment of this disorder.

Contents

Abbreviations: ICU, intensive care unit; TNF, tumor necrosis factor; IL, interleukin; MCP, monocyte chemoattractant protein; LPS, lipopolysaccharide; TLR, Toll-like receptor; NF-κB, nuclear factor-κB; COX, cyclooxygenase; iNOS, inducible nitric oxide synthase; CLP, cecal ligation and puncture; ODN, oligodeoxynucleotide; AP-1, activator protein-1; cAMP, cyclic AMP; CREB, cAMP response element binding protein; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling; siRNA, small interfering RNA; FADD, Fas-associated death domain; z-VAD-fmk, benzyloxycarbonil-Val-Ala-Asp fluoromethylketone; TF, tissue factor; NETs, neutrophil extracellular traps; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; PAF, platelet-activating factor; VEGF, vascular endothelial growth factor; S1P, sphingosine-1-phosphate; ARDS, acute respiratory distress syndrome; PPAR, peroxisome proliferator-activated receptor; PDE, phosphodiesterase; cGMP, cyclic GMP; COPD, chronic obstructive pulmonary disease; HMGB1, high mobility group B-1.

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1. Introduction

Sepsis, a syndrome that occurs when microbial invasion induces systemic illness, is one of the most common reasons for critically ill patients to be admitted to an intensive care unit (ICU) and, despite advances in modern hemodynamic, antibiotic, and ventilator clinical support, it represents a major clinical problem and remains the leading cause of death in the critically ill patient population (Angus et al., 2001; Angus & van der Poll, 2013; Wang, Shapiro, Angus, & Yealy, 2007). The development of a failure of one or more organs, including lung, kidney, and liver, poses a major threat to the survival of patients with sepsis, and mortality in sepsis is most often attributed to multiple organ dysfunction (Marshall et al., 1995). In the very recent past, the third international consensus definitions have been advocated for sepsis and septic shock. Thus, sepsis is now redefined as life-threatening organ dysfunction due to a dysregulated host response to infection (Singer et al., 2016).

The pathological process in the development of sepsis-induced multiple organ dysfunction leading to death remains incompletely understood. The pathogenesis of organ dysfunction in sepsis may be multifactorial. Sepsis has been defined as a systemic inflammatory syndrome, in which there is an identifiable focus of infection (Bone et al., 1992), and thus it has been believed that the immunoinflammatory system plays a pivotal role in the pathogenesis of multiple organ dysfunction (Wang & Ma, 2008). However, therapeutic strategies aimed at eliminating the inflammatory response have shown only modest clinical benefit. Indeed, in numerous clinical trials (Abraham et al., 2003; Marshall, 2000; Natanson, Esposito, & Banks, 1998; Opal et al., 2013; Ranieri et al., 2012; Zeni, Freeman, & Natanson, 1997), most of the therapies that modify inflammatory mediators have largely failed to reduce mortality in patients with severe sepsis, in which sepsis is complicated by acute organ dysfunction (Levy et al., 2003).

A better understanding of the molecular mechanisms involved in the pathogenesis of sepsis and its resultant organ failure is engaged on being sought, and the identification for development of therapies aimed at preventing or limiting molecular events associated with the progress of fatal organ failure, hence leading to improvement of outcomes, is an urgent issue. This review article provides an overview of candidate factors that have been proposed to comprise the pathological process of multiple organ dysfunction in sepsis. We will also introduce a number of fascinating therapeutic approaches to prevent the development of sepsis organ failure that have received much attention in recent years from the perspective of the potential value to be used as a novel therapeutic strategy, and thereupon will discuss a promising avenue for the management of this nasty disorder.

2. Cytokines in the pathophysiology underlying sepsis

The term “cytokine” is derived from a combination of two Greek words, “cyto” meaning cell and “kinos” meaning movement, and describes a large group of small protein molecules with low molecular weights (mostly <40 kDa) that function extensively cellular communication. Cytokines may be occasionally called by other names, including lymphokine (cytokines produced by lymphocytes), monokine (cytokines produced by monocytes), and chemokine (cytokines with chemotactic activity). Cytokines can be produced by a broad range of cells, but the predominant producers are macrophages and helper T cells. Cytokines may act on the cells that secrete them, on nearby cells, and on distant cells in an autocrine, paracrine, and endocrine fashion, respectively. They are often produced in a cascade, as one cytokine stimulates its target cells to make additional cytokines. The sequential release of specific cytokines is referred to as a “cytokine cascade” (Blackwell & Christman, 1996). Cytokines play pleiotropic roles in regulating the innate and adaptive immune systems (Oppenheim, 2001).

In the 1990s, the exacerbated release of prototypic inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein (MCP)-1, was believed to mediate many of immunopathological features in sepsis. The term “cytokine storm” thus arose, although it is not precisely defined (Matsuda & Hattori, 2006). A cytokine storm is a potentially fatal immune reaction consisting of a positive feedback loop between cytokines and immune cells. When the immune system is fighting against pathogens, cytokines signal immune cells, such as lymphocytes and macrophages, to travel to the inflammatory site. In addition, cytokines activate those cells, stimulating their further production of effector cytokines. Once this positive feedback loop becomes uncontrolled, tremendous amounts of immune cells could be activated in a single space, causing possible damage to nearby organs. Alternatively, cytokines leaking into the blood stream may induce damage to remote organs by activating inflammatory cells there. Thus, cytokine storms have potential to inflict dreadful damage to body organs.

In light of the above, treatment with agents that can cut off the redundant inflammatory cytokine network, such as IL-1 receptor antagonist, TNF-α neutralizing antibody, and TNF-α receptor-immunoglobulin fusion protein, may be useful in retarding or preventing the development of multiple organ failure in sepsis. However, such cytokine-targeted therapies for septic patients who may have dysfunction of one or more organs have not proven to be of clinical benefit in trials (Abraham et al., 1998, 2001; Fisher et al., 1994; Zeni et al., 1997). This may be because numerous cytokines and redundant inflammatory pathways are disorderly involved in the development of sepsis syndrome and organ dysfunction. In this regard, the disappointing result has been recently reported showing that eritoran, which antagonizes lipopolysaccharide (LPS) signaling as a blocker of MD2-Toll-like receptor (TLR) 4 and thereby is expected to inhibit the extreme reaction associated with an excessive and uncontrolled production of multiple inflammatory cytokines, has failed to demonstrate a significant benefit in a phase III clinical trial of patients with severe sepsis (originally defined as sepsis plus organ dysfunction) (Opal et al., 2013).

3. Induction of the transcription factor NF-κB in sepsis

Nuclear factor-κB (NF-κB) proteins comprise a family of structurally-related eukaryotic transcription factors that form dimers composed of the five mammalian Rel proteins and are typically a heterodimer of p50 and p65 subunit (Bäuerle & Baltimore, 1996). NF-κB plays as a central participant in inflammation through its ability to induce transcription of proinflammatory genes (Baldwin, 1996). NF-κB is activated by a huge array of stimuli (Gilmore, 2006; Hayden & Ghosh, 2004), including microbial pathogens, which are recognized by TLRs, and inflammatory cytokines, which are recognized by their specific membrane receptors such as the TNF receptor. In quiescent cells, NF-κB resides as a latent cytoplasmic complex bound to its inhibitory protein IκB (Baldwin, 1996; Bäuerle & Baltimore, 1996). Immune stimuli such as endotoxin triggers a series of signaling events that ultimately converge to activation of one or more redox-sensitive kinases that specifically phosphorylate IκB, resulting in IκB polyubiquitination and subsequent degradation, followed by liberation of NF-κB. NF-κB then translocates to the nucleus where it leads to the regulation of synthesis of multiple inflammatory molecules. Many of the proinflammatory genes are regulated by κB sites in the DNA (Pahl, 1999). Indeed, the genes encoding inflammatory mediators, including TNF-α, IL-6, cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), and adhesion molecules, have putative binding sites for NF-κB at their promoter sites to activate gene expression (Collins, 1993; Libermann & Baltimore, 1990; Rajapakse, Kim, Mendis, & Kim, 2008; Trede, Tsytsykova, Chatila, Goldfeld, & Geha, 1995). This highlights the pivotal role of NF-κB in immune and inflammatory responses and identifies it as a prime candidate for targeted inactivation. Thus, inhibition of NF-κB activation has been proposed as an attractive therapeutic option to prevent multiple organ injury and to improve survival in sepsis (Liu & Malik, 2006).

The effects of pharmacological interventions designed to inhibit activation of NF-κB have been examined in rodent models of LPS-induced