Advances in Sepsis Research

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KEYWORDS

• Sepsis • Innate immune receptors • Pathogen • Clearance • Edema • Vascular leak

KEY POINTS

- Treatment strategies targeting early pathophysiological alterations in sepsis improve outcomes.
- Pathogen toxins are triggers of inflammation in sepsis, and therapies aimed at enhancing toxin clearance represent potential complements to early antimicrobial therapy.
- The innate immune response is an early built-in host response to infecting pathogens. Treatments aimed at modifying this response have therapeutic potential.
- Vascular leak, secondary edema formation, and hypovolemia contribute to poor outcome in sepsis; several distinct pathophysiological mechanisms may be targeted to ameliorate this response.

INTRODUCTION

Of the World Health Organization top 10 causes of death, 4 fulfill the definition of sepsis (www.who.int). Sepsis occurs when infection results in systemic inflammation[1,2] and is termed severe sepsis when accompanied by new organ dysfunction. The 28-day mortality rate of severe sepsis is 15% to 30%,[3–6] which increases to 20% to 60% when complicated by arterial vasodilation and ventricular dysfunction, leading to septic shock.[7] The number of deaths due to severe sepsis and septic shock is greater than the number of deaths due to acute myocardial infarction, even in the Western world,[3] and continues to increase.[4] Effective treatment of severe sepsis can lead to complete resolution with no sequelae, whereas ineffective treatment is fatal or leads to long-term morbidities and increased long-term mortality rates; so timely effective therapy is crucial.[8]

Herein the authors consider aspects of the septic inflammatory response that provide novel targets for therapeutic intervention. Specifically, (1) clearance of inflammatory pathogen molecules from the circulation, (2) modulation of innate immune receptors and intracellular signaling, as well as (3) vascular leak are considered.

PATHOGENS AND PATHOGEN TOXINS

Targeting the host septic inflammatory response (eg, anti–tumor necrosis factor,[9] activated protein C [APC][5]) has not worked in more than 30 phase 3 randomized controlled trials (RCTs).[10–12] In contrast, simply targeting the pathogen by source control (draining the abscess, etc) and early broad-spectrum antibiotics is very effective. Kumar and colleagues[13] found that for every hour delay in antibiotic administration after onset of septic shock, mortality increased by 7%. Another

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less-established approach targeting the pathogen is to enhance clearance of toxins. Whether alive or dead, pathogens elicit an inflammatory response by release of toxins such as lipopolysaccharide (LPS) from gram-negative bacteria; the structurally similar glycolipid, lipoteichoic acid (LTA) from gram-positive bacteria; and other glycolipids such as phospholipomannan (PLM) from fungal pathogens.[14] These toxins bind to innate immune receptors (see section on Innate Immune Signaling Induced by Pathogen Toxins) to trigger a septic inflammatory response. Accordingly, clearance of pathogen toxins is an important, underrecognized, and modifiable aspect of sepsis management that complements effective antimicrobial therapy.

Pathogen Toxins Induce an Inflammatory Response

Septic shock is primarily due to release of pathogen toxins.[8] The lipid A domain of LPS binds Toll-like receptor 4 (TLR4) expressed on many cell lines, thereby inducing nuclear factor (NF)-κB signaling and the subsequent proinflammatory and antiinflammatory cytokine response.[15] LTA of gram-positive bacterial cell membranes is composed of a polyglycerolphosphate chain connected by a glycolipid moiety[16] and binds TLR2 and TLR6 to induce NF-κB signaling.[17] Fungal PLM is composed primarily of C24 hydroxy fatty acids linked to phytoceramide and phytosphingosine, with a hydrophilic polysaccharide domain consisting of mannose residues.[18] PLM and related glycolipids are ligands for TLR2, TLR4, and TLR6.

Sequestration as the Initial Step in Limiting the Adverse Effects of Pathogen Toxins

Pathogen toxins in the aqueous phase are quickly bound by transfer proteins that bind lipid moieties.[19] When transfer protein availability is limited, LPS incorporation into lipoproteins is reduced and LPS toxicity is increased, thus transfer proteins are the first step in sequestering pathogen toxins. LPS binding protein (LBP) and bactericidal permeability-increasing protein are homologous to the endogenous lipid transfer protein phospholipid transfer protein (PLTP), and all bind pathogen toxins.[19] LBP and PLTP bind LPS and transfer it from micelles or from LPS aggregates in the aqueous phase to high-density lipoprotein (HDL)[20,21] and other lipoproteins.[22] While LBP can bind and additionally transfer LPS to CD14, a cofactor in subsequent signaling via TLR4, PLTP does not transfer LPS to CD14[20] and, thus, does not trigger downstream inflammatory signaling. LBP more effectively transfers LPS from bacterial cell wall fragments to lipoproteins than PLTP.

Following binding by transfer proteins, LPS is transferred to and sequestered within HDL and, after LBP and PLTP-facilitated transfer, within low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL).[23] LPS, LTA, and even the LPS lipid A analog, eritoran,[24] are distributed primarily on HDL (~60%) with the remainder on LDL and VLDL particles. In sepsis, this distribution shifts from the predominant HDL carriage of LPS to increased LDL and VLDL carriage of LPS.

Subsequent Clearance of Pathogen Toxins from the Circulating Lipoprotein Compartment

Pathogen toxins are then cleared primarily by hepatic uptake and excretion in bile.[25] Characterization of the exact mechanisms of hepatic clearance of pathogen toxins is limited but likely involves the LDL receptor (LDLR). LDLR knockout mice have increased mortality after cecal ligation and puncture compared with mice with intact LDLR[26] suggesting a central LDLR role in pathogen toxin clearance.

Further support for the role of LDLR in pathogen toxin clearance is provided by recent observations that PCSK9 decreases LPS clearance and increases the innate immune response to pathogen toxins.[27] Circulating PCSK9, produced primarily by the liver, binds LDLR expressed on hepatocytes and, upon internalization of the LDLR complex, targets it for lysosomal degradation so that it is not recycled back to the hepatocyte cell surface (**Fig. 1**). Thus, increased PCSK9 activity decreases LDLR expression of hepatocytes, whereas reduced PCSK9 activity results in increased LDLR expression and increases pathogen toxin clearance, decreases cytokine inflammatory response, and improves survival from sepsis. This effect is lost in LDLR knockout in mice and by an LDLR genetic variant that interferes with binding of PCSK9 to the LDLR.[27] Taken together, these data support the hypothesis that pathogen toxin clearance depends substantially on PCSK9 and the LDLR.

How This Knowledge May Lead to Innovative Therapeutic Strategies

Mechanisms of pathogen toxin clearance may be novel targets for treatment. PCSK9 inhibition to increase pathogen toxin clearance conceivably could decrease the inflammatory response and improve survival in human sepsis. PCSK9 inhibition targets the pathogen and like antibiotics, may be particularly effective.