Sepsis is a systemic inflammatory response syndrome triggered by infection. The hallmarks of clinical sepsis are a broad range of systemic and organ function aberrations, including core temperature (hyperthermia or hypothermia), cardiac (rate and contractility), and respiratory and hemodynamic perturbations. When sepsis results in at least 1 organ failure or dysfunction, it is classified as severe sepsis. Severe sepsis with hypotension unresponsive to fluid resuscitation defines septic shock. Sepsis syndrome afflicts almost 750,000 patients in the United States each year, at a cost of almost $17 billion, and causes more than 200,000 deaths annually. The incidence of sepsis syndrome continues to rise along with the increase in life span and several other important risk factors. Sepsis without organ dysfunction is a relatively benign condition, and spontaneous recovery with conservative measures results in low in-hospital mortality (5% to 10%). Severe sepsis without organ dysfunction is a relatively benign condition, and spontaneous recovery with conservative measures results in low in-hospital mortality (5% to 10%). Severe sepsis and septic shock carry high mortality, 30% to 50%, in severe cases by dysregulation of immune competencies leading to a compromised host defense condition and increased risk for mortality.

The hemostasis system plays a major role in the pathophysiology of sepsis and septic shock. The intrinsic clotting factors, the fibrinolytic cascade, platelets, and tissue-derived clotting factors (such as tissue factor) are rapidly activated and persist along the entire evolution of the syndrome. The dysregulation of the hemostasis system is closely linked to the inflammatory cells and cytokine response. TNF-α and other factors stimulate tissue factor expression in macrophages and endothelium, leading to augmented coagulopathy via the extrinsic coagulation pathway, whereas certain coagulation factors, such as thrombin and factor Xa, possess proinflammatory actions via specific receptors. The importance of the hemostasis and inflammation systems in severe sepsis has recently been further recognized following the marginal therapeutic efficacy of activated protein C, which is now approved by the FDA for treatment of severe sepsis.

Abnormalities in Toll-like receptor-4 and its signaling kinase, IRAK-4, have been associated with worse outcomes. The alarming increase in pathogens resistant to antibiotics that, in the past, were very effective in prevention and treatment of sepsis no doubt contributes to increases in severe sepsis prevalence in the elderly. The key mechanisms believed to initiate and propagate sepsis syndromes are inflammatory mediators that are elicited by the action of toxins released from the pathogen. Most prominent among these factors are the cytokines, released from monocytes and tissue macrophages and innate cellular immune defense elements. These cytokines trigger numerous additional proinflammatory events in all organs, leading to widespread organ dysfunction. However, it is now also recognized that other cytokines, such as IL-10, IL-13, and transforming growth factor-β, elicit a compensatory antiinflammatory response syndrome that is marked by depressed activity of B cells, T cells, and macrophages and modulation of numerous genomic and posttranscriptional pathways. The compensatory antiinflammatory response syndrome response is believed to contribute to severe cases by dysregulation of immune competencies leading to a compromised host defense condition and increased risk for mortality.

Cardiac RAGE in Sepsis
Call TOLL Free for Anti-RAGE
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TNF-α, IL-1, IL-6, IL-8, and macrophage inflammatory protein. Anti-HMGBl antibodies provided dose-dependent protection against endotoxemia and sepsis models in rodents. Anti-HMGBl treatments hold the promise for efficacy in treatment sepsis at an extended “therapeutic window.” The role of RAGE in mediating diverse vascular and cardiac pathophysiological processes has also well documented.

Over this context, Boyd et al.10 report on a seminal observation that has the potential to bear significantly on new opportunities for translational medicine of their discoveries into treatment of a major cause of morbidity and mortality from sepsis and septic shock cardiac dysfunction, heart failure, and cardiogenic shock. The authors set to explore the missing link between the known cardiac-depressing activities of the key inflammatory cytokine signaling system, the Toll-like receptors that has already been implicated in suppression of cardiac contractility.11 The discovery stemmed from an elegant group of in vitro and in vivo studies that identified a new role for S100A8 and S100A9, 2 known members of the S100 EF-hand family of proteins. Members of this family have already been implicated in cardiac function and especially contractile performance, such as S100A1 protein.12–13 S100A8/9 have also been implicated in inflammation via RAGE signaling cascade,14,15 and, hence, the authors postulated that, like other members of the S100 proteins, S100A8/9 may have a role in cardiac dysregulation of contractility in association of inflammatory condition such as sepsis. The authors have set to explore their hypothesis under conditions of potent proinflammatory stimulus, lipopolysaccharide endotoxin stimulation of cardiac cells in vitro and simulation of sepsis by endotoxin in mice. The highlights of their findings include the identification of the S100A8/9 proteins to be products of inflammatory challenge to cardiac cells; the likely apocrine/autocrine actions of the S100A8/9 protein via the RAGE receptor to suppress cardiac contractility (likely by modulation of intracellular Ca2+ fluxes and the association of the S100A8/9 with SERCA2a and ryanodine receptor 2 complex). Considering that S100A8/9 are products of the inflammatory challenged cardiac cells, the authors conclude that a local circuit of cardio-depression is elicited in the sepsis syndrome thereby afflicting direct organ (cardiac) failure.

However, important caveats need be pointed out. The in vivo model used in the study does not necessarily represent the human septic shock syndrome because the authors used pure lipopolysaccharide administered in high pharmacological doses. In humans, sepsis evolves following pathogen infections that deteriorates into septic shock over several days or weeks and is associated with pathogens that release diverse toxins. Furthermore, these experimental data have not yet been confirmed in humans or in experimental models in which neutralization of the S100A8/9 proteins is introduced after the onset of sepsis, leading to improved cardiac performance and survival benefits.

The data generated in this report may have over-arching implications for treatment of septic shock in general and cardiac dysfunction in particular. The data suggest that S100A8/9 proteins could play a role in broad, multigain failure thereby significantly contribute to septic shock. This action of S100A8/9 exacerbate cardiac (and possibly other organs) failure independently from the systemic derangements. Thus, effective inter-ventions in S100A8/9 proteins production or actions (via antibodies, small molecules or other modalities) could provide new therapeutic strategies to alleviate multiple organ failures that underwrite septic shock and death.

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Disclosures

None.

References


Key Words: sepsis ■ S100A8/9 ■ RAGE ■ cardiac failure ■ Toll-like receptor