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Review

DAMPs activating innate immune responses in sepsis

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ABSTRACT

Sepsis refers to the deleterious and non-resolving systemic inflammatory response of the host to microbial infection and is the leading cause of death in intensive care units. The pathogenesis of sepsis is highly complex. It is principally attributable to dysregulation of the innate immune system. Damage-associated molecular patterns (DAMPs) are actively secreted by innate immune cells and/or released passively by injured or damaged cells in response to infection or injury. In the present review, we highlight emerging evidence that supports the notion that extracellular DAMPs act as crucial proinflammatory danger signals. Furthermore, we discuss the potential of a wide array of DAMPs as therapeutic targets in sepsis.

Contents

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1. Introduction

Sepsis was first described by Hippocrates in 400 BC as follows: 'In acute diseases, coldness of the extremities is a very bad sign'. In modern medical science, treatment of diseases begins with identification. The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference held in 1991 defined sepsis as systemic inflammatory response syndrome (SIRS) induced by infection. Severe sepsis is characterized by sepsis complicated by organ dysfunction. Septic shock is defined as severe sepsis plus a state of acute circulatory failure characterized by persistent arterial hypotension. Dramatic increase in the incidence of sepsis over the past few decades has been fueled in part by the increase in the number of invasive surgical techniques performed over this time period (from 164,072 in 1979 to 659,935 in 2000) (Martin et al., 2003). Despite a better understanding of the pathophysiology of sepsis and advances in medical care, sepsis remains the most challenging problem in intensive care units (ICUs) (Husak et al., 2010).

Sepsis is particularly common in the elderly. Both incidence and mortality are significantly greater in older individuals than in other groups (Angus and Wax, 2001; Dombrovskiy et al., 2007; Martin et al., 2006). Angus et al. (2001) reported that the average age of incidence of severe sepsis was 64 years of age in US. The average age of septic patients has been increasing steadily over time (Martin et al., 2003). Although sepsis is a serious, life-threatening disease, recognition of this problem is very low compared to other age-associated diseases. Addressing this issue is urgent, because healthcare costs for the elderly are expected to rise as life expectancy increases. Survival in older septic patients often requires additional care in long-term care facilities to regain functional status. However, few studies have investigated sepsis in elderly patients. Moreover, it is estimated that among all published studies using animal models of sepsis, less than 1% used appropriately aged animals introducing a serious disconnect interpretation of sepsis studies using human or animals (Starr and Saito, 2014).

2. The innate immune system: the first line of defense

The innate immune system functions as a sentinel by rapidly detecting infections upon injurious insult. This results in activation of the adaptive immune system, which mounts an antigen-specific response (Scott and Saleh, 2007). Inflammatory cytokines are essential components of the innate immune response and are involved in tissue immunity. Although cytokines are necessary initially for bacterial clearance, excessive production of inflammatory cytokines can lead to multiple organ dysfunction syndrome (MODS) and, ultimately, death. Tumor necrosis factor (TNF)-α and interleukin (IL)-1 activate immune cells, leading to the production of inflammatory mediators such as cytokines, chemokines, and reactive oxygen species (ROS) (Castellheim et al., 2009). Numerous trials of anti-inflammatory agents designed to block the proinflammatory cascade have been performed. However, the failure of these trials has led investigators to question whether the reason for death of septic patients is uncontrolled inflammation. In 2003, Hotchkiss and Karl (2003) reported that after early activation of immune cells, their activity was down-regulated, leading to a state of immunosuppression and increased risk of secondary infection. Following the onset of hypo-inflammatory response, immunosuppressive state dominates which is characterized as immune cell death and shift Th1 cytokine to Th2 cytokine production (Sundar and Sires, 2013). More than 70% of septic patients died after three days of the disorder with unresolved septic foci and those patients had striking apoptosis-induced loss of cells of the innate and adaptive immune system including CD4 and CD8 T, B, and dendritic cells (DCs) (Hotchkiss et al., 2013). It is also well documented that human septic patients exhibit lymphocyte apoptosis, which is associated with a poor outcome (Le Tulzo et al., 2002), and these results are supported by more profound splenic and gut epithelial apoptosis after CLP in aged mice (Turnbull et al., 2004). Several immune-enhancing agents such as granulocyte-macrophage colony-stimulating factor have shown benefit in phase 2 clinical trials (Hall et al., 2011; Meisel et al., 2009). In light of the above, the balance between proinflammatory and anti-inflammatory response may be a critical target for sepsis care.

Both innate and adaptive immune responses are dysregulated by aging, which largely accounts for the increased incidence of infection in the elderly (De Gaudio et al., 2009; Grubeck-Loebenstein et al., 1998; Miller, 1996; West et al., 1989). A defective adaptive immune response has long been thought to be the cause for decreased immune function in the elderly. However, studies within the last decade have shown that multiple age-related changes in cells of the innate immune system are also responsible (Dewan et al., 2012). Within the innate immune system, although cell numbers appear maintained in old-age, macrophages or neutrophils may undergo functional alterations such as reduced antibacterial defense or ROS overproduction (Gomez et al., 2008). Furthermore, response to endotoxins in the elderly, which is characterized by profound hypotension, excess epinephrine response, delayed recovery of blood pressure, and an elevated cytokine response, is more severe than in younger subjects (Krabbe et al., 2001).

A number of studies over the past few decades have sought to define the key aspects of the innate immune response responsible for inducing host response to pathogens. Innate immunity was initially thought to involve non-specific recognition of microbes. However, the discovery of toll-like receptors (TLRs) in the 1990s indicated that pathogen recognition by the innate immune system was specifically mediated by pattern recognition receptors (PRRs). PRRs can be classified on the basis of their ligand specificity, function, and cellular localization. After the discovery of TLRs, several families of PRRs, including nod-like receptors (NLRs), C-type lectin receptors, and RIG-I-like receptors were identified. Receptor for advanced glycation end products (RAGE) was recently recognized as a crucial PRR family member involved in the pathogenesis of sepsis (Lutterloh et al., 2007; van Zoelen et al., 2009). Indeed, decoy receptors for TLR4 or the soluble receptor for AGE (sRAGE) were shown to recognize their respective ligands with high affinity and specificity, but were structurally incapable of inflammatory signaling or presenting the agonist to signaling receptor complexes in sepsis (Bopp et al., 2008; Jung et al., 2009).

PRRs, which are expressed by innate immune cells such as macrophages and DCs, recognize highly conserved components called pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides (LPS) of gram-negative bacteria, peptidoglycan of gram-positive bacteria, and other cellular components including microbial DNA, RNA, and bacterial flagellin. However, PAMPs alone cannot explain specific PRR activation during rejection of transplantation, spontaneous regression of occasional tumors, or most autoimmune disorders. Since Matzinger and co-workers suggested that innate immune cells could be tuned to endogenous danger