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Invited review

Immunotherapy: A promising approach to reverse sepsis-induced immunosuppression

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ABSTRACT

Sepsis is defined as life-threatening organ dysfunction caused by dysregulated host responses to infection (Third International Consensus definition for Sepsis and septic shock). Despite decades of research, sepsis remains the leading cause of death in intensive care units. More than 40 clinical trials, most of which have targeted the sepsis-associated pro-inflammatory response, have failed. Thus, antibiotics and fluid resuscitation remain the mainstays of supportive care and there is intense need to discover and develop novel, targeted therapies to treat sepsis. Both pre-clinical and clinical studies over the past decade demonstrate unequivocally that sepsis not only causes hyper-inflammation, but also leads to simultaneous adaptive immune system dysfunction and impaired antimicrobial immunity. Evidences for immunosuppression include immune cell depletion (T cells most affected), compromised T cell effector functions, T cell exhaustion, impaired antigen presentation, increased susceptibility to opportunistic nosocomial infections, dysregulated cytokine secretion, and reactivation of latent viruses. Therefore, targeting immunosuppression provides a logical approach to treat protracted sepsis. Numerous pre-clinical studies using immunomodulatory agents such as interleukin-7, anti-programmed cell death 1 antibody (anti-PD-1), anti-programmed cell death 1 ligand antibody (anti-PD-L1), and others have demonstrated reversal of T cell dysfunction and improved survival. Therefore, identifying immunosuppressed patients with the help of specific biomarkers and administering specific immunomodulators holds significant potential for sepsis therapy in the future. This review focusses on T cell dysfunction during sepsis and discusses the potential immunotherapeutic agents to boost T cell function during sepsis and improve host resistance to infection.

Contents

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1. Introduction

Sepsis is associated with a high morbidity and mortality, and is the most common cause of death among critically ill patients in non-coronary intensive care units [1]. According to the earlier consensus criteria guidelines of 1992 and 2001, sepsis was defined as a systemic response to documented or suspected infection manifested by two or more of the systemic inflammatory response syndrome (SIRS) criteria as a result of infection: temperature >38 or <36; heart rate >90 beats per minute; respiratory rate >20 breaths per minute; and white blood cell count >12,000/cu mm or <4000/cu mm, or >10% immature (band) forms [2]. Accordingly, severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension and septic shock as sepsis induced hypotension which is not corrected by adequate resuscitation and pressor support along with presence of perfusion abnormalities [2]. Sepsis and severe sepsis account for an estimated 20.7 million and 10.7 million cases per year worldwide, respectively, and may contribute to up to 5.3 million deaths worldwide per annum [3]. The recently formulated guidelines by the third international consensus definition for sepsis and septic shock (Sepsis-3) define sepsis as life-threatening organ dysfunction caused by dysregulated host responses to infection [4]. Currently, there is no definitive therapy to treat sepsis and physicians must rely on supportive care alone in the form of antibiotics and fluid resuscitation. Care for septic patients costs approximately $17 billion in the United States alone [5] and undoubtedly much more worldwide. Moreover, the incidence of sepsis is increasing at an alarming rate in the ageing population, who have inadequate immune responses as a consequence of immunosenescence [6].

Numerous clinical trials have failed to yield any novel therapeutics for sepsis. A hyper-inflammatory response characterized by excessive release of pro-inflammatory mediators such as TNF-α and interleukin-1, was thought to be the hallmark of sepsis and the most viable therapeutic target based on numerous pre-clinical and clinical studies [7]. On the contrary, clinical trials that have targeted pro-inflammatory mediators using agents such as anti-endotoxin (LPS, Lipopolysaccharide) antibodies, pro-inflammatory cytokine (TNFα, IL-1β) blocking antibodies and inhibitors, and TLR (Toll like receptor) antagonists have been disappointing [8–10]. Thus, the foundation of current sepsis treatment is supportive and consists of timely antibiotic administration, fluid resuscitation and organ system support. That strategy has attenuated early deaths among septic patients and improved overall survival [11,12]. Yet, despite these improvements, severe sepsis and septic shock still result in mortality rates of more than 30% [13].

Extensive research and better understanding of the immunological alterations during sepsis during the past decade, has revealed a role for immunosuppression in the pathogenesis of sepsis [11,14,15]. Historically, sepsis was considered to be composed of an initial hyper-inflammatory phase (SIRS) followed by an anti-inflammatory or immunosuppressive phase (counter anti-inflammatory response syndrome, CARS) [7,16]. This biphasic paradigm has been challenged by numerous recent reports, and it has now become evident that pro-inflammatory and anti-inflammatory phases can occur during variable time points during sepsis [17,18]. Currently, immunosuppression during sepsis is a topic of intense research among numerous laboratories worldwide. Indeed, various studies show that patients surviving the initial inflammatory phase of sepsis are highly susceptible to nosocomial infections with opportunistic organisms and suffer late deaths among initial sepsis survivors [19,20]. Although modern medicine strategies have resulted in improving the short term patient outcome in septic patients, it has equally resulted in a more protracted disease state with a shift towards immunosuppressive phenotype causing increased incidence of delayed deaths. In fact, greater than 70% of deaths occur after the 3 days of sepsis initiation, many of which occur weeks after sepsis onset [20]. More recent studies indicate that patients discharged from the hospital after sepsis have a high one year mortality rate, often due to the development of secondary infections [3,15]. With respect to the increasing findings of a shift in the time frame of mortality after sepsis, which can occur even years after initial septic insult, a trimodal distribution of deaths after sepsis has been recently postulated [15]. The three postulated phases include: early deaths due to inflammatory response, late deaths due to persistent organ injury and immunosuppression and delayed long term deaths (beyond 60–90 days post sepsis) due to persistent immune dysfunction and inflammation in the presence of other co-morbidities and advanced age [15]. It is important to note that, immune dysfunction or suppression is increasingly being recognized to play a critical role even in the pathology of delayed deaths after sepsis. Postmortem studies of patients who die of sepsis indeed have revealed marked immunosuppression [21] and pre-clinical studies equally support these findings [22–24]. Research by Hotchkiss et al. and others, have consistently shown that defects in effective adaptive immune system responses are a hallmark of immunosuppression during sepsis [11,14,16]. Immunotherapeutic strategies aimed at stimulating the immune system hold significant potential to reverse sepsis-induced immunosuppression and improve patient outcomes. The focus of this review is to highlight the major alterations in adaptive immune responses during sepsis, and the current and future potential for novel immunotherapeutic agents targeting reversal of T cell dysfunction.

2. Introduction to the adaptive immune system

The adaptive immune system is composed of cells that respond in a highly specific manner to the particular antigen that induced them. It is composed of specialized cells known as lymphocytes, specifically T and B lymphocytes, which mediate the cell- and humoral immune responses respectively. Fig. 1 shows a brief overview of various cells of the adaptive immune system. T cells play an important role in the elimination of infecting pathogens [25]. Innate immune cells such as dendritic cells, macrophages and monocytes prime naïve T cells by presenting specific pathogen-specific antigens in conjunction with major histocompatibility complex (MHC) class I and class II molecules [26]. Naïve T cells upon