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Review Article

Sepsis-Induced Immunosuppression: The Role of Co-inhibitory Molecules

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Abstract

Sepsis is one of the most common cause of death among hospitalized patients in the intensive care unit (ICU), with current therapeutic options falling short of a comprehensive solution. The condition's pathophysiology is marked by a spectrum of immunological impairments, with a growing consensus that immunosuppression plays a decisive role in the condition's rising morbidity and mortality rates. Extensive preclinical and clinical research has identified the upregulation of several co-inhibitory molecules during sepsis, including Programmed Death-1 (PD-1), Programmed Death Ligand-1 (PD-L1), Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4), B and T Lymphocyte Attenuator (BTLA), T Cell Membrane Protein-3 (TIM-3), and Lymphocyte Activation Gene-3 (LAG-3). These molecules, which exert a significant inhibitory effect on T cell function, are believed to contribute to the immunosuppressive state induced by sepsis. The elucidation of the intricate mechanisms by which these molecules induce immunosuppression is essential for devising the most efficacious treatment strategies for sepsis. The burgeoning field of immunotherapy, particularly the blockade of co-inhibitory molecules, represents a significant frontier in sepsis research. This approach holds substantial promise for the future of sepsis therapy, warranting further exploration and clinical investigation to harness its potential fully.

Keywords

Sepsis, Immunosuppression, Co-inhibitory Molecules, PD-1, PD-L1, CTLA-4, BTLA, TIM -3, LAG-3, Immunotherapy

1. Introduction

Sepsis is defined as a life-threatening organ dysfunction that is caused by a dysregulated host response to infection., according to the third international consensus definition for sepsis and septic shock [1], is a leading cause of death in critically ill patients. According to the World Health Organization (WHO) report in 2018, sepsis is estimated to affect more than 30 million people worldwide per year, even leading to 6 million deaths, extrapolated from a systematic review of published national and local population [2].

There is no definitive therapy that targets the underlying pathobiology of sepsis exists, so antibiotics, fluid resuscitation and organ support remain the mainstay of treatment. On 26 May 2017, the World Health Assembly and the World Health Organization declared sepsis a global health priority by adopting a resolution to improve the prevention, diagnosis and management of this deadly disease. This marked a great

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progress in the global fight against sepsis [2].

Classically, the time course of sepsis is characterized by pro-inflammatory and anti-inflammatory phases that occur during variable time points after sepsis. However, evidences from recent studies has indicated that, after the initial pro-inflammatory phase, sepsis is assumed to be severe immunosuppression, which is an important cause of deterioration in patients [3]. Some immunopathologic mechanisms have been reported to be involved in sepsis-induced immune alterations affecting both innate and adaptive immunities [4]. These alterations positively correlated with immunosuppression [5]. One of the important mechanisms for immunosuppression is hypothesized to be increased expression of Co-inhibitory molecules including PD-1, PD-L1, CTLA-4, BTLA, TIM-3 and LAG-3, so inhibiting these molecules is widely considered to be a key step for the treatment of sepsis. The individual Co-inhibitory molecules and their roles in sepsis immunopathology were discussed as follows.

2. Programmed Death-1 (PD-1) and Its Ligands PD-L1/PD-L2

The programmed death-1 (PD-1) receptor, discovered in 1992, is a 228-amino-acid molecule, 50–55 kDa monomeric type I transmembrane glycoprotein. It is a member of the B7−CD28 superfamily, composed of an extracellular immunoglobulin Variable-type (V-type) extracellular domain, a transmembrane domain and a cytoplasmic tail which executes the intracellular signaling. The intracellular region of PD-1 receptor is composed of immuno-receptor tyrosine-based inhibitory motif (ITIM) and immuno-receptor tyrosine-based switch motif (ITSM) [6]. PD-1 is encoded by the *Pdcd1* gene on chromosome 1 in mice and chromosome 2 in human. Human and murine PD-1 proteins share approximately 60% of the amino acid sequence [7]. PD-1 is known to be up-regulated on the surface of activated CD4+ and CD8+ T cells usually to limit their hyper-activation and uncontrolled inflammation. Furthermore, the sustained up-regulation of PD-1 when facing heavy antigen load in severe infection, leads to impairment of both innate and adaptive immune responses [2, 7]. It is well known that PD-1 has two ligands, named PD-L1/B7-H1/ CD274 and PD-L2/B7-DC/CD273 [7-9]. PD-L1 is known to be expressed both on immune as well as non-immune cells, while PD-L2 is expressed only on immune cells [9, 10].

Over the past decades, numerous studies have shown a sustained increase in PD-1 and PD-L1 expression on various immune cells during sepsis. In a pre-clinical study by Wang et al. reported that the mice deficient in PD-1 have increased bacterial clearance and improved survival in experimental sepsis induced by cecal ligation and puncture (CLP) and the CLP-induced sepsis cause a significant increase in PD-1 expression on Kuppfer cells in liver (a type of resident macrophages), while PD-1-deficient Kuppfer cells displayed markedly increased phagocytic capacity and restoration of immune functions. [8]. Huang et al. found that PD-L1-deficient mice showed a remarkable reduction in multiple organ damage and inflammatory cytokine levels in circulation or at infectious site when compared with wild-type mice and CLP mice showed higher percentage of circulating neutrophils positive for PD-L1 expression which correlated with lethal outcomes [9]. A postmortem study involved sepsis patients by Boomer et al. found that T cell function was evidently impaired in association with over-expression of PD-1 receptor and activation of marker CD69, and a significant decrease in IL-7 receptor and CD28 expression (a co-stimulatory T cell receptor); and increased PD-L1 and PD-L2 expression on dendritic cell. This study also indicated that these Co−inhibitory molecules may be potential targets in the treatment of sepsis [2] Chen et al. found that CLP-induced sepsis cause PD-1 expression increasing apparently on CD4+ and CD8+ T cells in splenic, which was correlated with impaired T cell function [10]. The majority of these studies showed that PD-1/PD-L1 plays a critical role in T cell dysfunction and in innate immune cell impairment during sepsis.

The Co-inhibitory molecules interaction often leads to T cell exhaustion, with impaired effector T cell functions, decreased cytokine production, decreased proliferative capacity and increased apoptosis [11]. Furthermore, it has been reported that inhibit this interaction can reverse sepsis-induced immunosuppression and improve host resistance to infection. Therefore, targeting either PD-1 or PD-L1 seems a rational approach to restoring host immune responses and improving outcomes. Antibodies targeting PD-1 and PD-L1 have been studied widely. A study by Chang et al. showed that in vitro blockade of the PD-1: PD-L1 pathway decreases apoptosis and improves interferon-γ (IFN-γ) and intereukin-2 production by CD8+ T lymphocytes from septic patients [12]. Another more important study by Patera et al. reported that ex vivo incubation of septic patient's whole blood with anti-PD-L1 antibody significantly improved phagocytic function of neutrophils and monocytes, and restored CD8+ T cell and NK cell functions; with most beneficial effects seen among patient groups with lowest baseline function of these cells [13]. A recent research by Shindo et al. demonstrated that a unique anti-PD-L1 peptide (termed as compound 8) double the survival rate in a two hit model of CLP-induced sepsis followed by Candida albicans-induced fungal infection [14]. A study by Chang et al. showed that even a delayed treatment with anti-PD-L1 up to 24–48 h after the onset of fungal sepsis, could reverse T cell dysfunction, increase MHC II on antigen presenting cells and significantly improve survival [15]. Similar to anti-PD-L1, anti-PD1 is also protective during fungal sepsis. A Study in a two hit model of CLP followed by Candida albicans fungal sepsis by Shindo et al showed that treatment with anti-PD-1 improved MHC II expression on splenic macrophages and dendritic cells, and a combination therapy with interleukin-7 increased interferon-γ (IFN-γ) secretion by CD4+ and CD8+ T cells, and anti-PD-1 had no effect on either proliferation and CD28 expression on CD4+ and CD8+ T cells [16]. A multicen-

ter trial for evaluating the dose safety, pharmacokinetics and pharmacodynamics of anti-PD-L1 (BMS-936559 of Bristol–Myers Squibb) in septic patients has been completed recently, its results are awaited (ClinicalTrial.gov# NCT02576457). Overall the above studies prove that blocking the PD-1/PD-L1 interaction with blocking antibodies against each restores immune function among immunosuppressed septic host and provides significant protection. The discovery of PD-1/PD-L1 pathway blocking antibodies also has been a boon to cancer therapy that various pharmaceutical companies have been approved by Food Drug Administration to produce the new drugs for cancers [17, 18]. These therapy has successfully induced regression of some advanced-stage cancers and improved survival rate.

3. Cytotoxic T Lymphocyte Antigen-4 (CTLA-4)

CTLA-4 gene is discovered in 1987 when screening mouse killer T cell cDNA libraries by Brunet et al [17]. CTLA-4 also known as CD152, which shares 30% homology to the T cell co-stimulatory molecule CD28, is up-regulated in T cells after activation and plays an significant negative regulatory role in the immune system [11]. CTLA−4 transmitting an inhibitory signal to T−cell and preventing T−cell activation by binds CD80 and CD86. The mechanism of CTLA-4 to inhibit T lymphocyte proliferation and activation involves reduction in IL-2 production and IL-2 receptor expression and arresting T cells at the G1 phase of the cell cycle [19, 20]. Therefore, factors which result in sustained up-regulation of CTLA-4 would compromise T cell immune response and render the host immunosuppressed. And inhibition of CTLA-4 with blocking antibodies might help restore T cell functions. In previous study, Inoue et al. demonstrated that in CLP-induced sepsis model, CTLA-4 expression was progressively increased on both CD4+ and CD8+ T cells and regulatory T cells, starting at 24 h after induction of sepsis, along with T cell apoptosis and depletion [21], furthermore treatment with anti-CTLA-4 has a dosage-depend effect on survival where high dose (200 μg per mouse) worsened survival while low-dose (50 μg per mouse) improved survival in two different strain of mice (C57BL6 and CD-1 mice). Chang et al. using two model of sepsis including a primary Candida albicans fungal sepsis and a two hit model (CLP-induced sepsis followed by Candida albicans), demonstrated that anti-CTLA-4 increases T lymphocyte IFN-γ production, and significantly improves survival [15]. In clinical studies, the CTLA−4 expression of CD4 T−cells was significantly higher in septic patients than non-septic patients which indicate that it is a potential target for sepsis therapy [22, 23]. However, studies addressing the role of CTLA-4 during sepsis are limited, further study needs to be performed to confirm the effect of the anti-CTLA−4 in sepsis.

4. B and T Lymphocyte Attenuator (BTLA)

BTLA is not only expressed on T−cells and B−cells, but also on natural killer cells, macrophages and dendritic cells. BTLA interacts with tumor necrosis factor superfamily molecule, termed herpes virus entry mediator (HVEM) and known to cause inhibition of T cell exhaustion [11]. A study by Shubin et al. reported that BTLA expression on T cells correlated with increased mortality in a rodent model of sepsis. In accordance with these findings, Shubin et al. further demonstrated that increased BTLA expression on peripheral CD4+ T cells among critically ill sepsis patients positively correlated with development of subsequent nosocomial infections. Furthermore, the previous study also showed that BTLA deficient mice (BTLA−/−) had increased numbers of CD4+ T cells in the spleen following sepsis and implicated a role for BTLA in apoptosis induced T cell loss. Another study by Shubin, using a septic CLP mouse model showed that BTLA expression facilitates impairment of innate inflammatory cell activation and promotes MHC II reduction, increases bacterial burden following CLP, increases circulating interleukin-10 levels, and results in multi-organ injury and decreased survival; as compared to septic BTLA knockout mice [24]. These results indicated that BTLA could be used as a biomarker and mediator of sepsis−induced immunosuppression. However, different results were later found in a clinical study. Interestingly, it has been reported that anti-BTLA monoclonal antibody is known to be having dual effects including blocking as well as potentiating effects on BTLA mediated effects [25, 26]. Currently, only one study has evaluated the effect of ant-BTLA antibody in a two hit model of hemorrhage followed by sepsis. This study by Cheng et al. found that, treatment with anti-BTLA (at a dose of 25 μg per gram body weight) caused excessive inflammatory immune responses, increased organ injury, leading to significantly increased morbidity and mortality [27]. These results demonstrate that anti-BTLA actually further potentiated BTLA actions in the model of sepsis. The contradictory results may be explained by the different population included in each phase of sepsis. Therefore, further studies need to be performed to confirm the function of anti-BTLA in sepsis.

5. T Cell Membrane Protein-3 (TIM-3)

TIM-3/CD366 was first described as a marker of activated IFNc-producing T cells [28]. TIM-3 interacts with CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) and Galectin 9. Comparing to other inhibitory molecules discussed above, TIM-3 has not been extensively investigated in sepsis yet. In vivo study, interaction of TIM-3 with its ligand galectin-9 has been shown to cause T cell death and tolerance [29]. TIM-3 is often co-expressed with PD-1 on severely exhausted T cells [30], where both receptors act

synergistically to suppress immune functions [31, 32]. It was demonstrated that blockade of TIM-3 partially restored those impaired T-cell functions [33-35]. However, some recent pre-clinical studies have shown that blocking TIM-3 exacerbates sepsis. Zhao et al. demonstrated that blocking TIM-3 signal with soluble TIM-3-Immunoglubulin (sTIM-3-IgG) resulted in exacerbation of sepsis, inducing macrophage pro-inflammatory responses and lymphocyte apoptosis during acute phase and enhancing anti-inflammatory phenotype for macrophages and CD4+ T cells during later stage of sepsis [36]. This study also showed that blocking TIM-3 signaling increased sepsis severity and significantly decreased survival in a septic CLP model. This finding was correlated with the role of TIM-3 in negatively regulating toll like receptor-4 mediated responses of macrophages leading to inhibition of macrophage activation, which showed TLR4 signaling pathway an important mediator of TIM-3 related immune homeostatic mechanisms during sepsis [37]. However, another clinical study by Ren et al. showed that TIM-3 expression on monocytes was significantly elevated among sepsis patients as compared to severe sepsis, septic shock and control patients; and soluble TIM-3 (sTIM-3) levels in plasma of septic shock group was higher than sepsis or severe sepsis group, which was correlated with eventual non-survivors [38].

6. Lymphocyte Activation-Gene-3 (LAG-3)

LAG-3 (CD223), a member of the immunoglobulin superfamily, as well as a CD4-like protein, bounded to MHC-II molecules and was up-regulated during inflammation [39]. The exact mechanism of action of LAG-3 is still unclear. LAG-3 is mostly expressed on anergic and exhausted T cells, often in strong association with PD-1 [40, 41]. Neutralizing antibodies against LAG-3 can only partially reverse anergy and rescue immune dysfunction [42, 43], but combined anti-LAG-3/ PD-1 approaches have demonstrated strong immune restoration [44], suggesting that LAG-3 inhibitory activity alone may be gentler than other inhibitory checkpoints. Therefore, LAG-3 may be a novel therapeutic target during sepsis and further studies are needed to discover the exact mechanism of LAG-3.

7. Immunotherapy in Sepsis-induced Immunosuppression

In addition to antibiotic and other sepsis therapy strategies, immunotherapy may be another effective approach to improve the outcome of septic patients. However, the immunological responses of sepsis are too complex to be characterized by one simple immune method. Excessive inflammation and immunosuppression both can induce poor outcome in sepsis, it is difficult to decreasing excessive inflammation or boosting host immunity. According to previous clinical studies, it is imperative to understand that no single targeted therapy would fit all septic patients and individualized therapy is extremely important. Therefore, judging the immune status of sepsis patients is crucial to choose immunotherapy. At present, HLA−DR has been studied deepest and might be an optimal clinical marker to judging the immune status of sepsis patients [45]. Appropriate patient selection is the key to finding the right therapy. This was well demonstrated by a recent reanalysis of an original phase III clinical trial data which showed that infusion of recombinant human IL-1 receptor antagonist failed to reduce mortality among severe sepsis patients [46]. However, when the results of the same study were reanalyzed for subgroups of septic patients with characteristics of macrophage activation syndrome, there was a significant positive impact of treatment on survival among this specific group of patients [47]. Another example is the use of anti-TIM-3 antibody during sepsis. Rodent models have shown that treatment with anti-TIM-3 potentiates inflammation and increases mortality during sepsis [36]. Additionally, combination therapies including Co-inhibitory molecules inhibitors and other therapies such as monophosphoryl lipid A, interleukin-7, interelukin-15, IFN-γ and FMS like tyrosine kinase-3 ligand might be more appropriate for specific patients and this will lead to better attenuation of sepsis induced immunosuppression [48-50]. Furthermore, it is important that Co-inhibitory molecules blockade therapy should be targeted to patients who actually manifest an increased expression of these molecules. The dose of Co-inhibitory molecules inhibitors also needs to be well titrated, as a higher dose might precipitate untoward effects and lead to a severe inflammatory response and increased mortality. Further study of human need to be performed to grow our confidence in using Co-inhibitory molecules inhibitors for sepsis therapy.

8. Conclusion

In conclusion, immunosuppression induced by sepsis is very common and Co-inhibitory molecules expressed on T−cell surface plays a significant role in this mechanism. Pre-clinical and clinical studies have shown that targeting these Co-inhibitory molecules could improve survival in sepsis, which indicates that these Co-inhibitory molecules may be potential targets for sepsis treatment. However, such a therapy needs to be individualized based on immune status of a particular patient; and cautious treatment with individual or a combination of co-inhibitory molecules inhibitors in the future for sepsis therapy.

Abbreviations

PD-1	Programmed Death-1
PD-L1	Programmed Death Ligand-1
CTLA-4	Cytotoxic T-Lymphocyte Antigen-4

BTLA	B and T Lymphocyte Attenuator
TIM-3	T Cell Membrane Protein-3
LAG-3	Lymphocyte Activation Gene-3

Conflicts of Interest

The authors declare no conflicts of interest.

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