Review Article

Programmed Cell Death-1/Programmed Death-ligand 1 Pathway: A New Target for Sepsis

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Abstract

Objective: Sepsis remains a leading cause of death in many Intensive Care Units worldwide. Immunosuppression has been a primary focus of sepsis research as a key pathophysiological mechanism. Given the important role of the negative costimulatory molecules programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1) in the occurrence of immunosuppression during sepsis, we reviewed literatures related to the PD-1/PD-L1 pathway to examine its potential as a new target for sepsis treatment.

Data Sources: Studies of the association between PD-1/PD-L1 and sepsis published up to January 31, 2017, were obtained by searching the PubMed database.

Study Selection: English language studies, including those based on animal models, clinical research, and reviews, with data related to PD-1/PD-L1 and sepsis, were evaluated.

Results: Immunomodulatory therapeutics could reverse the deactivation of immune cells caused by sepsis and restore immune cell activation and function. Blockade of the PD-1/PD-L1 pathway could reduce the exhaustion of T-cells and enhance the proliferation and activation of T-cells.

Conclusions: The anti-PD-1/PD-L1 pathway shows promise as a new target for sepsis treatment. This review provides a basis for clinical trials and future studies aimed at revaluating the efficacy and safety of this targeted approach.

Key words: Immunosuppression; Programmed Cell Death-1; Programmed Death-ligand 1; Sepsis

Introduction

Sepsis is a major threat to human health. One of the main clinical characteristics of sepsis is a decreased ability to eradicate primary pathogens and an increased risk of secondary nosocomial infection.[1] However, the development of secondary infection is usually mediated by weakly virulent, and even opportunistic organisms, such as *Stenotrophomonas*, *Acinetobacter, Enterococcus, Pseudomonas*, and *Candida*, indicating a common state of immunosuppression in patients with sepsis.[1,2] Despite considerable progress in the development of antibiotics and recovery strategies,[3,4] an effective treatment for sepsis is still lacking.

Negative costimulatory molecules, including programmed cell death-1 (PD-1), cytotoxic T lymphocyte antigen-4 (CTLA-4), and B and T lymphocyte attenuator, constitute a complicated immune regulatory system, negatively regulating the activity of immune cells. Studies have shown that negative costimulatory molecules are involved in the occurrence and development of the immunosuppression of sepsis.[5] PD-1, as a negative costimulatory molecule, binds to its ligand programmed death-ligand 1 (PD-L1) to deliver an inhibitory signal that restrains the activation, proliferation, and effector functions of immune cells.[6,7] Excessive PD-1 expression and exhausted T-cells have been observed in patients with sepsis,[8,9] and blockade of PD-1 or its ligand (PD-L1) can reverse T-cell dysfunction and enhance pathogen clearance.[10] Thus, we expect that the PD-1/PD-L1

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pathway may become a new target for the treatment of sepsis. This review highlights this potential clinical breakthrough based on research focusing on the following aspects: immunosuppression in sepsis, PD-1/PD-L1 pathway properties suggesting its role in immunomodulation in sepsis, PD-1/PD-L1 expression changes during sepsis, the application of anti-PD-1/PD-L1 treatment, and limitations of anti-PD-1/PD-L1 treatment in sepsis.

Immunosuppression in Sepsis

Despite considerable efforts to promote the early identification and treatment of sepsis, the occurrence of sepsis-induced multiple organ failure, prolonged Intensive Care Unit stays, frequent progression to death, and incomplete recovery are still major issues, emphasizing the need for new research directions to determine the proximal mechanisms underlying sepsis.[11] High spiking fevers, tachycardia, shock, and dyspnea are characteristics of sepsis. Owing to this striking presentation, the prevailing theory for many years was that sepsis represents an uncontrolled inflammatory response.[12] Numerous anticytokine and anti-inflammatory agents have failed to show benefits or, in some cases, reduced survival rates.[13,14] The failures of these immunomodulatory agents, such as anti-endotoxin (lipopolysaccharide), anti-tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and toll-like receptor-4 inhibitors,[15-17] imply that the pathophysiological process of sepsis is not only the sequelae of an uncontrolled proinflammatory response to infectious challenge, but also a more complex condition in which multiple mediators are released, inducing a highly multifaceted immunological and host tissue response.

Further, contrary to previous contentions, recent data provide evidence that both proinflammatory and anti-inflammatory stages of the host immune response to injury and/or sepsis occur concomitantly.[18] In general, an initial hyperinflammatory phase predominates after sepsis initiation. However, in fact, more than 70% of the sepsis-related deaths occur after the first 3 days, many of which occur weeks after sepsis onset.[1] Although patients may die in either the hyperinflammatory or the hypoinflammatory phase of sepsis, new therapies and treatment protocols have resulted in prolonged disease with a shift toward the immunosuppressive phase.[11] In addition, sepsis is increasingly a disease of elder people whose immune systems are often impaired.[19] Thus, sepsis-induced immunosuppression has been recognized as the major course leading to high mortality in patients with sepsis. Adequate evidence supports a central role for immunosuppression in sepsis. Meakins *et al*.[20] first noted that patients who had a delayed-type hypersensitivity response had an increased risk for sepsis and sepsis-related mortality, indicating that patients with sepsis had a hyposensitivity to antigen stimulation. Lymphopenia, a potential factor involved in the severe immunosuppression of sepsis, occurs rapidly and early during sepsis.[21] A reduction in lymphocytes decreases the number of immune cells available to combat infection. In addition, in both animal models and human patient samples, there is a significant loss of dendritic cells and epithelial cells and deactivation of monocytes during sepsis.[22-24] Even after complete recovery, many patients who recover from sepsis still have long-lasting impairment of the immune system and increased mortality.[25] Therefore, targeting immunosuppression provides a logical approach to treat protracted sepsis; administering specific immunomodulatory agents holds significant potential for sepsis therapy in the future.[26] The majority of immune cell loss and dysfunction has also been associated with the phenotypic change characterized by decreased human leukocyte antigen-DR expression and increased inhibitor-receptor expression.[27,28] Thus, changes in these immunophenotypic markers may be useful for the identification of patients with sepsis who have impaired immunity and are candidates for trials of immunoadjuvant therapies.[29,30]

Programmed Cell Death-1/Programmed Death-Ligand 1 Pathway Properties Suggesting Its Role in Immunomodulation in Sepsis

A recently recognized mechanism of immunosuppression in sepsis is T-cell exhaustion.[29] T-cell exhaustion was first described in mice suffering from chronic viral infections[31] and was subsequently shown to occur in other mouse models of infection as well as in humans afflicted with HIV, hepatitis C virus, hepatitis B virus, and cancer.[32-35] T-cell exhaustion is a state of T-cell dysfunction occurring during chronic infections and cancer.[36] These exhausted T-cells are commonly defined by a progressive loss of T-cell effector function, an alert transcriptional state distinct from that of functional effector or memory T-cells.[36] Another cardinal feature of T-cell exhaustion is the overexpression of multiple inhibitory receptors, such as PD-1, CTLA-4, lymphocyte activation gen-3, T-cell immunoglobulin mucin-3, and CD160.[36,37] Exhaustion of T-cells prevents optimal control of invasive antigens and tumors. Of note, exhausted T-cells are not inert. These exhausted cells remain suboptimal functions that limit ongoing pathogen replication and tumor progression. Furthermore, revitalization of exhausted T-cells can reinvigorate immunity with enhanced ability to eliminate invading pathogen and control progressing tumor cells.[38-41]

Although many of these mechanisms contribute to T-cell exhaustion, PD-1 and its two ligands (PD-L1/PD-L2) are thought to play key roles.[42] PD-1 was first identified as an apoptosis-associated molecule in 1992.[43] However, subsequent experiments did not confirm the direct involvement of PD-1 in programmed cell death.[44] Thus far, it has been accepted that PD-1 receptors, inducible coinhibitory cell-surface proteins expressed on T- and B-cells, constitute a complex system of negative regulators involved in controlling T-cell responses.[45] PD-1 engagement with its ligands plays an important role in maintaining autoimmune tolerance and preventing the occurrence of autoimmune diseases under physiological conditions.[46]

However, PD-1 and its ligands are usually upregulated on the surface of antigen-specific T-cells exposed to the chronicity of cancer and persistent infections, leading to cellular exhaustion and abrogation of effector functions.[47] Indeed, blocking of PD-1 pathway has resulted in successful enhancement of T-cell immunity against viral pathogens and tumors.[48] A better understanding of PD-1-related molecule expression may provide further insight into sepsis-induced immunosuppression, especially "T-cell exhaustion".

PD-1 and its two ligands, PD-L1 and PD-L2, belong to the B7:CD28 family.[49] PD-L2 expression is limited to relatively few cells and tissues.[50] In contrast, PD-L1 is broadly expressed on B-cells, dendritic cells, macrophages, culture bone marrow-derived mast cells, and T-cells.[50] Furthermore, PD-L1 is further upregulated in response to their activation. It is highly likely that the much more diverse expression of PD-L1 than PD-L2 is important with respect to their applications as therapeutic target. Thus, PD-1/PD-L1 pathway as the potential target for immunotherapy has been more investigated. Although T-cell exhaustion can partially explain the high morbidity and mortality in sepsis, reversal of exhausted T-cells by the blocking PD-1/PD-L1 pathway can lead to pathogen clearance and improve survival in clinically relevant models of sepsis.[51,52] Since PD-1 was first described in a PD-1 knockout mouse model, which developed a spontaneous lupus-like autoimmune disease, interest in the locus has increased.[53] Subsequently, numerous studies have demonstrated that this "checkpoint blockade" of the PD-1/PD-L1 pathway is important for T-cell regulation in a variety of infectious, autoimmune, and cancer models in mice.[46] Thus, the PD-1/PD-L1 pathway has an important role in regulating T-cell responses, and this provides a basis for the development of a new generation of targeted therapies against PD-1 and PD-L1. Although the most encouraging observations have been obtained in the context of viral infection and cancer, there is a significant relationship between the PD-1/PD-L1 pathway and immunosuppression in sepsis.

The PD-1/PD-L1 pathway acts on intermediate molecules in the T-cell receptor (TCR) signaling pathway, such as PI3K, Akt, ZAK-70, and PKC-θ, thereby interrupting the transduction of TCR signals to ultimately inhibit the activation and proliferation of T lymphocytes.[54] Furthermore, the PD-1/PD-L1 pathway can indirectly inhibit the activation and proliferation of T-cells by reducing the synthesis of IL-2 and the anti-apoptotic factor B-cell lymphoma-extra large, contributing to the apoptosis of T-cells.[46] The deactivation of immune cells, a signature of immunosuppression, is characterized by the weakened reactivity or even nonresponse to antigenic stimulation, and decreased ability and effector function for cytokine secretion.[27] The overexpression of PD-1 and PD-L1 on immune cells results in the deactivation of these cells, accelerates the process of apoptosis, and thus participates in the occurrence and development of immunosuppression in sepsis. Guignant *et al*.[55] found that the proliferation of lymphocytes is decreased in the peripheral blood of patients with septic shock, in a manner that is correlated with the overexpression of PD-1 or PD-L1 in lymphocytes. Furthermore, the overexpression of PD-1 and PD-L1 is associated with the occurrence of nosocomial infection. This indicates that PD-1 and PD-L1 overexpression induced by sepsis triggers a decrease in the proliferation of T-cells, leading to the incompetence of T-cells. Condotta *et al*.[56] showed that the increased expression of negative costimulatory molecules, including PD-1, on CD8+ T-cells accelerated the exhaustion of CD8+ T-cells and depressed the secretion of effector molecules (interferon-gamma and TNF-α).

Moreover, the autopsy reports of patients with sepsis have confirmed that negative costimulatory molecules, such as PD-1, play important roles in immunosuppression. First, uncontrolled infection was observed in the autopsy tissues of patients. Although patients with sepsis were typically treated with broad-spectrum antibiotics and other methods to control infection, their ability to eradicate primary pathogens remains low, and the risk of hospital-acquired secondary infections is high. This tendency alone clearly demonstrates that the immune function of patients with sepsis is substantially reduced. Second, the secretion of splenocytes in patients who die from sepsis is significantly decreased, with a 10% reduction compared to secretion in a control group; however, the expression of negative costimulatory molecules, such as PD-1, on CD4+ T lymphocytes is significantly increased.[29] This implies that PD-1 participates in the deactivation of immune cells, which is likely a major contributor to the low immunological function in patients with sepsis. Since there is abundant evidence for the important role of the PD-1/PD-L1 pathway in the initiation and promotion of immunosuppression, the blockade of the PD-1/PD-L1 pathway is promising as a new therapeutic target for sepsis immunotherapy.

Changes in Programmed Cell Death-1/Programmed Death-ligand 1 Expression in Sepsis

While the PD-1/PD-L1 pathway plays an important role in maintaining autoimmune tolerance and preventing the occurrence of autoimmune diseases under physiological conditions,[46] it is best understood in the context of its role in viral infections and cancer.[57,58] Sepsis and cancer share many immunology defects, and therefore, investigations of the immune system in cancer may facilitate the development of immunotherapy strategies for sepsis. In the early stage of sepsis, PD-1 expression tends to increase, suggesting that it has favorable effects by avoiding excessive inflammation and reducing organ damage induced by sepsis. However, the overexpression of PD-1 can inhibit host immunity, leading to the occurrence of immunosuppression.[11] In a mouse model of cecal ligation and puncture, the expression levels of PD-1 and PD-L1 were significantly increased in T

and B lymphocytes, monocytes, and dendritic cells.[51,52] In addition, another study showed that while PD-1 expression on CD4+ and CD8+ T lymphocytes continuously increased with the progression of sepsis, the numbers of CD4+ and CD8+ T-cells substantially decreased.[51] Furthermore, studies have shown that the expression levels of PD-1 and PD-L1 on CD4+ and CD8+ T-cells and monocytes also increased in the peripheral blood of patients with septic shock.[8,55] Moreover, increased PD-1 and PD-L1 expression levels have also been observed in injured organs induced by sepsis.[59-61] These observations clearly demonstrate that PD-1 and PD-L1 expression levels are significantly increased in sepsis. Furthermore, a recent study from our group demonstrated a significant correlation between the increased expression of PD-1/PD-L1 and immunosuppression in sepsis, and monocyte PD-L1 expression served as an independent predictor of 28-day mortality in septic shock patients.[62] Therefore, monitoring changes in PD-1 and PD-L1 expression in sepsis might have important clinical significance for prognostic prediction.[62-64]

Research on the Blockade of the Programmed Cell Death-1/Programmed Death-ligand 1 Pathway

Viral and tumor cells take advantage of the PD-1/PD-L1 pathway to escape host immune defenses.[65-67] These findings built a solid foundation for the development of anti-PD-1 pathway as immunotherapeutic approaches. The clinical application of anti-PD-1 and/or PD-L1 antibodies in patients with cancer has demonstrated significant effects,[68,69] and FDA has recently approved two PD-1 monoclonal antibodies to treat human cancers, one from Bristol-Myers Squibb (Opdivo or nivolumab) and another from Merck (Keytruda or pembrolizumab).[70] Sepsis and tumors share similar mechanisms with respect to immunosuppression, prompting researchers to evaluate the effect of the blockade of the PD-1/PD-L1 pathway on sepsis.[11] Brahmamdam *et al*.[51] reported that an anti-PD-1 antibody could prevent the reduction of lymphocytes and dendritic cells in a mouse model of sepsis, and improved the survival rate of the mice. Furthermore, Zhang *et al*.[52] showed that injecting anti-PD-L1 antibodies to mice suffering from sepsis could reduce the apoptosis of lymphocytes and increase TNF-α and IL-6 secretion, while reducing IL-10 secretion; moreover, the survival rate of the mice was significantly increased. Zhang *et al*.[8] further demonstrated that an anti-PD-L1 antibody could reduce the apoptosis of T lymphocytes in the peripheral blood of patients with sepsis, and improved the ability of monocytes to secrete TNF-α and IL-6, while reducing IL-10 production. A recent study showed that a novel short-acting anti-PD-L1 peptide (compound 8) significantly improved survival in a clinically relevant immunosuppressive model of sepsis.[71] Anti-PD-1 and anti-PD-L1 antibodies are different from each other with respect to their mechanisms of action. However, studies have shown that blocking different coinhibitory molecules might exert a synergistic effect on immunotherapy for sepsis.[56,72,73] With respect to the appropriate timing for anti-PD-1/PD-L1 antibody administration, Brahmamdam *et al*.[51] showed that when the anti-PD-1 antibody was given to mice 24 h after the induction of sepsis, the survival rate increased. These findings are promising for the clinical use of anti-PD-1 antibodies in sepsis treatment. Most patients with sepsis cannot be diagnosed in a timely manner for various reasons; therefore, this delayed drug administration can significantly increase the probability that patients with sepsis can be successfully treated and cured.

Before anti-PD-1/PD-L1 antibodies are used in clinical settings, it is worth considering whether they are suitable for all patients with sepsis. According to a recent study, an anti-PD-L1 antibody restores the functions of cytomegalovirus-specific T lymphocytes in patients with kidney transplantation showing high expression of PD-1 but does not have a restorative effect in patients with low PD-1 expression or in a control group.[73] Our group showed that the PD-L1 expression in monocytes was an independent predictive factor of the 28-day mortality risk of sepsis, and the combination of the SOFA and SAPS II scores could improve the predictive ability of PD-L1 as a marker of the 28-day mortality.[62] Therefore, patients with high PD-L1 expression in monocytes should be considered to be in a state of immunosuppression, and treatment with anti-PD-1/PD-L1 antibodies was expected to be effective in such cases.[74] Thus, indictors of the effectiveness of anti-PD-1/PD-L1 antibody treatment should include increased expression of PD-1 on T lymphocytes and elevated expression of PD-L1 on monocytes. In addition, rare *in vivo* experiments have examined the use of anti-PD-1/PD-L1 antibodies in patients with sepsis to date. Accordingly, despite their potential, further studies are necessary to determine the mechanism of action and safety of anti-PD-1/PD-L1 antibodies before they can be applied in clinical settings.

Limitations of Anti-programmed Cell Death-1/Programmed Death-ligand 1 Treatment in Sepsis

Although encouraging results of anti-PD-1/PD-L1 therapy have been gained from preclinical studies in sepsis, there is still no any direct clinical study confirm the efficacy on septic patients up to now. Thus, limitations of antibody therapies aimed at blocking PD-1/PD-L1 pathway, especially considerations in safety, should be taken into account before their applications clinically. First, the biggest fear is the development of an exaggerated inflammatory response which can lead to a fatal destruction for patients with sepsis, because both PD-1 and PD-L1 KO mice are autoimmune prone when they are challenged with autoantigens.[75] Antibody therapy-associated adverse events, such as diarrhea, pneumonitis, type 1 diabetes, and others, have been reported in clinical trials in cancer.[47] However, these clinical observations of anti-PD-1/PD-L1 therapy have

proven that efficacy of such immune agents against tumors compensated for acceptable and manageable side effects observed in a small fraction of patients.[47] Furthermore, patients with sepsis typically may not require as prolonged therapies with anti-PD-1/PD-L1 treatment as patients with cancer. Therefore, severe autoimmune reactions will likely be less of a problem in patients with sepsis. Second, it is essential to stratify patients based on their immune status and administer personalized immunotherapy for individual patients. In addition to anti-PD-1/PD-L1 antibodies, other immunomodulatory agents targeted at boosting immune responses have shown potential effects in treatment of sepsis, such as recombinant human IL-7, IL-15, interferon gamma, and anti-CTLA antibody.[26] These suggest that blockade of PD-1/PD-L1 pathway is not the all but only a part which can restore the immunity of patients with sepsis. As mentioned above, lack of PD-1 and/or PD-L1 upregulation in tumor-infiltrating immune cells or tumor cells in patients showed a poor clinical response to PD-1/PD-L1 checkpoint blockade therapy.[76,77] As a consequence, one important issue if we are to give anti-PD-1/PD-L1 therapy to septic patients is to identify the right patient that could benefit from such therapy because it is unlikely, due to well-established heterogeneity of septic patients, that blocking a given immune checkpoint will be a magic bullet for all.[74] Therefore, immunotherapy targeted at blockade of PD-1/PD-L1 pathway needs to be directed toward patients who are actually immunosuppressed and have high levels of PD-1 and/or PD-L1 expression on immune cells.[78] Specific patient populations may be identified with the help of specific biomarkers. Thus, robust standardized tools for patients' stratification are highly desirable. Finally, circles when would be the appropriate time to administer such therapy in septic patients remain a question. According evidence is scarce to date. Further investigation should be administered to resolve this issue.

Conclusions

The PD-1/PD-L1 pathway plays key roles in triggering the immunosuppression of sepsis. The overexpression of PD-1/PD-L1 induced by sepsis causes the deactivation of immune cells, leading to immunosuppression. Although the immune state of patients with sepsis is complex and variable, high PD-1/PD-L1 expression on the surfaces of a variety of immune cells is a common clinical finding. Therefore, inhibiting the PD-1/PD-L1 pathway might promote the recovery of immune cell functions and ultimately improve the survival rate of patients with sepsis. Of course, extensive clinical trials are needed to confirm this hypothesis. However, the PD-1/PD-L1 pathway certainly has great potential as a new target for the treatment of sepsis.

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Conflicts of interest

There are no conflicts of interest.

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