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Deregulation of T cell response in sepsis

Xianghong Yang[1], Bangchuan Hu[2], Renhua Sun[2], Jianghua Chen[1]

[1]Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, 310003, P.R. China, [2]Intensive care unit, Zhejiang Provincial People's Hospital, Hangzhou, 310014, P.R. China

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1. ABSTRACT

The development of sepsis invovles the dysfunction of immunity due to an imbalance between the hyperimmune response and the immunoparalysis. Immune cells in both the innate and acquired immune system, including neutrophils, macrophages, dendritic cells, T cells and NK cells, are actively involved in the process. The interaction between immune cells, proinflammatory and anti-inflammatory cytokines contribute to the immunoparalysis in sepsis. Abnormal $CD4^+$ and $CD8^+$ T cell responses are major components of the deregulated acquired immune response in sepsis. Immune dysfunction of regulatory T cells (Tregs) contributes to the pathogensis of sepsis. Furthermore, IL-7 is essential for the replenishment and survival of T cells, which represents a promising target for immunotherapy of sepsis. In this review, we discusse the the immunoparalysis in the sepsis, with a focus on the deregulation of T cell response.

2. INTRODUCTION-

Sepsis is one of the most significant problems among patients in intensive care unit (ICU), approximately 40 % of patients in ICU occur sepsis. Sepsis causes millions of deaths globally each year. It is responsible for more than 210,000 deaths among more than 750,000 suffered ones annually in the United States alone (1). Pathogenesis of severe sepsis involves a cascade of cytokines leading to the clinical syndrome of hypotension, multiple organ failure and, sometimes, death (2). During this process, proinflammatory response is not effectively counterbalanced by the anti-inflammatory response, resulting in an uncontrolled hyperimmune response and subsequent cellular dysfunction. Meanwhile, the hyperimmune response is accompanied by a state of immunosuppression or immunoparalysis developed after the initial proinflammatory process.

The immunoparalysis is caused by the apoptosis of immune cells and high levels of anti-inflammatory cytokines, which serve to inhibit the activation and functions of lymphocytes and macrophages, and suppress the production of proinflammatory cytokines. Currently, the exact connections between the initial hyperimmune response, immunoparalysis and mortality of septic shock are not clear, but it is known that immunoparalysis impairs the capacity of the organism to maintain a "healthy" inflammatory process and the capability to clear pathogens properly (3). Although the degree of imbalance between the hyperimmune response and the immunoparalysis varies during the course of disease progression in each individual, as well as among different patients (3-5), evidences have demonstrated that deregulation of the immune response is involved in the development of sepsis.

In septic patients, T cell receptor (TCR) diversity is decreased after the onset of shock, which is associated with high mortality of sepsis (6), suggesting that impaired T cell clonal activation and expansion may link to the immunoparalysis and the aggravation of sepsis. However, though TCR plays a key role in immune recognition, depletion of T cells with a TCR specific antibody does not result in the immunoparalysis observed in septic patients (7). Therefore, the role of T cell-mediated immune dysfunction in the pathogenesis of sepsis is complicated and needs further investigation. In this review, we reviewed the recent advances in this field**.**

3. IMMUNE DYSFUNCTION IN SEPSIS

The imbalance between the hyperimmune response and immunoparalysis contributes to the morbidity and mortality of sepsis. The mechanism of immune dysfunction involves deregulation of innate immune response and adaptive immune response mediated by immune cells such as neutrophils, macrophages, dendritic cells, T cells, NK cells and inflammatory cytokines secreted by these cell populations. Toll-like receptors (TLRs) are a class of proteins that play a fundamental role in pathogen recognition and activation of innate immunity, thus involve in the pathogenesis of sepsis. For example, in a murine model of sepsis, TLR2 deficiency improves the survival rate of septic mice by promoting efficient bacterial clearance and restoring a proinflammatory cytokine balance in the lung. The results suggest that TLR2 may induce the innate immune dysfunction (8). TLR4 also plays a pivotal role in sepsis. Lipopolysaccharide (LPS), the ligand of TLR4, has been found to be associated with the severity of sepsis and the high mortality rate seen in septic shock. Binding of LPS to TLR4 can activate macrophages in a TLR4-PI3K-AKT-NF-κB dependent manner, consequently, activated macrophages elicit and amplify the systemic inflammatory response in sepsis, Interestingly, a recent study demonstrated that T cell immunoglobulin and the mucin domain protein 3 (Tim-3) restored homeostasis of sepsis by negatively regulating the TLR4 mediated responses (9).

The imbalance between the production of proinflammatory and anti-inflammatory cytokines links to the pathogenesis of sepsis. For example, dendritic cells (DCs) from septic mice displayed an impaired capacity to release the pro-inflammatory and Th1-promoting cytokines such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and (interleukin) IL-12 in response to bacterial stimuli, but secreted abundant IL-10 (10). IL-10 is the most relevant inhibitor of IL-12 production, but detailed analysis showed that endogenous IL-10 was not responsible for dampening IL-12 secretion in DCs. IFN-γ plus GM-CSF treatment induced secretion of IL-12 in DCs isolated from mice at early septic stage but not late septic stage, whereas splenic macrophages from mice at late septic stage can produce more TNF-α in response to GM-CSF stimulation (10). Interestingly, Pène *et al*. demonstrated that adoptive transfer of bone marrow-derived DCs (BMDCs) reversed sepsis-induced immune dysfunction in a model of secondary *P. aeruginosa* pneumonia. Mechanistic study showed that BMDCs did not enhanced antibacterial activity, but delayed neutrophil recruitment, strongly attenuated the early peak of TNF-α and restored an adequate Il-12p70/IL-10 balance in septic mice (11). Song *et al*. also reported that in septic mice, splenic T-cell p38 MAPK activation and IL-10 release was increased, whereas release of Th1 cytokines such as IL-2 and IFN-γ was repressed. Inducible NO synthase (iNOS) gene deficiency inhibited p38 MAPK activation in T cells isolated from septic mice and suppressed IL-10 release in macrophages, but it only partially restored IL-1 release and had no effect on IL-12 production (12). The data suggest that nitric oxide (NO) release from iNOS regulates sepsis-induced immune dysfunction associated with cytokines involved in both innate and acquired immune response.

Transforming growth factor (TGF)-β also involves in the pathogenesis of sepsis. Ahmad *et al*. found that in a rat model of Gram-negative bacterial sepsis, the circulating levels of TGF-β increased dramatically, which was mainly produced by macrophages. Moreover, TGF-β suppressed IL-2 production and proliferation of T cells in a paracrine manner (13). In hemorrhaged mice, TGF-β, IL-6 or eicosanoid-induced IL-4 can induce T cells to secrete IL-10, which suppressed T-cell proliferation (Figure 1). Given the fact that macrophages can also produce IL-10, IL-10 bridges the innate and acquired immune response (14). IL-15 has a similar role in association with both innate and adaptive immune response. IL-15 can inhibit sepsis-induced apoptosis of immune cells including NK cells, dendritic cells, CD8 T cells and gut epithelial via increasing the abundance of antiapoptotic BCL-2 while decreasing proapoptotic Bim and PUMA, thus reversing innate and adaptive immune dysfunction and improving survival in sepsis (15).

Heffernan *et al*. demonstrated that sepsis-inducing invariant natural killer T cells (iNKT) cells emigrated to the peritoneal cavity from the liver, whereas programmed death-1(PD-1)-deficient iNKT cells failed to demonstrate similar migration. Moreover, iNKT (-/-) mice displayed dysfunctional macrophage phagocytosis and altered peritoneal bacterial load, whereas the phenotype was

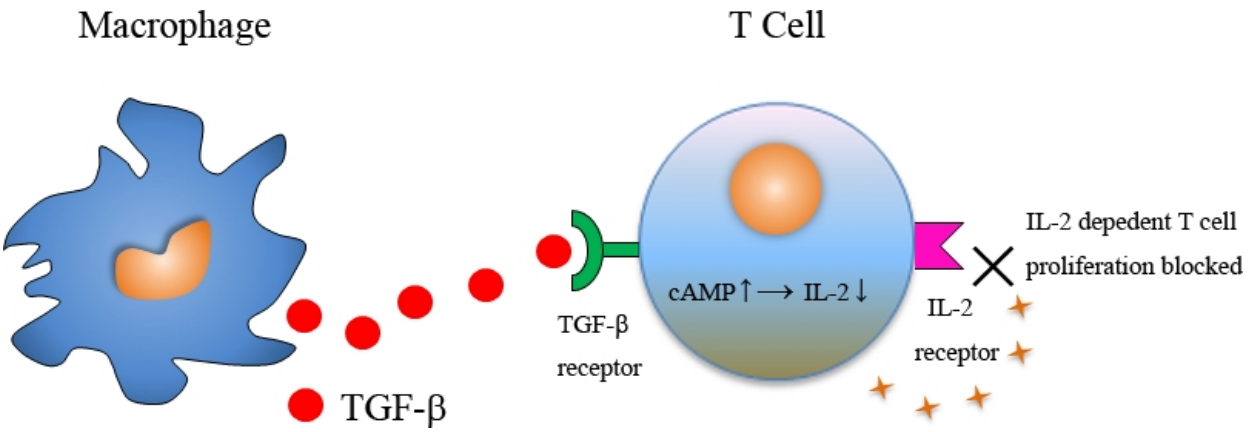

Figure 1. Macrophages regulate T cell function. Splenic macrophages secrete TGF-β to inhibit IL-2 production and proliferation of T cells in a paracrine manner. Up-regulation of cAMP is required for blocking the TCR signaling mediated proliferation (?).

reversed when peritoneal macrophages from iNKT(-/-) mice were cocultured with wild-type iNKT cells. The data suggested that peritoneal iNKT cells mediated innate immune cellular and inflammatory responses to sepsis and peritonitis through regulating peritoneal macrophage phagocytic activity (16).

4. DEREGULATION OF T CELL RESPONSE IN SEPSIS

Prostaglandins (PGs) are small-molecule derivatives of arachidonic acid (AA) that are produced by cyclooxygenases (COX, including the constitutively active cyclooxygenase COX1 and the inducible COX2) and PG synthases (17). IL-2 plays a central role in the growth, proliferation, and differentiation of T cells. A significant suppression of IL-2 production by T cells in septic rats was observed as compared with those from sterile and control rats. Detailed analyses showed that PGE2 inhibited IL-2 production by T cells (18). Interestingly, The inhibitory effect was reversed by a COX-2 inhibitor (the name of the inhibitor, NS398?) (19). Moreover, pretreatment of neonatal rats with NS398 also abrogated the suppression of ConA-mediated [Ca(2+)](i) response in T-cells (20). These findings suggest that PGE2 suppresses T-cell-mediated immune function by attenuating T-cell Ca(2+) signaling in sepsis (Figure 2).

During sepsis, apoptosis of lymphocytes is likely to be a consequence of the down-regulation of inflammatory processes. The extensive apoptotic death of lymphocytes may contribute to profound immunosuppression in sepsis. Intriguingly, it has been demonstrated that augmentation of canonical NF-κB activity in lymphocytes can reduce apoptosis of T cells, alleviate immunosuppression during murine sepsis, and improve survival of septic mice (21). More recently, another transcription factor, peroxisome proliferator-activated receptor gamma, was found to induce T cell apoptosis through inhibiting both the antiapoptotic BCL-2 expression and prosurvival PI3K/Akt signaling, which resulted in a breakdown of defense mechanisms occurs during systemic inflammation of sepsis, and an increased mortality of septic mice (22).

Immune imbalance associated with sepsis is represented by abnormal numbers of T cell subsets. For example, Tschaikowsky *et al*, found that both absolute lymphocyte counts and the CD4+/CD8+ T-cell ratio were increased significantly in septic patients as compared with those of healthy controls. Particularly, CD4+ and CD8+ T-cell counts in nonsurvivors of sepsis were approximately twice as high as those of survivors (23). However, in a recent study, patients one day after the onset of sepsis had decreased CD3+ and CD4+T lymphocyte percentages, as well as decreased CD4+/CD8+ T cell ratio, which are associated with the severity of sepsis (24). Recently, by using a murine septic model, Condotta *et al*. found that sepsis induced a rapid loss of naive CD8+ T cells. Moreover, the impairment of the capability of naive CD8+ T cells to respond to viral and bacterial infection was sustained for months after sepsis induction, suggesting that sepsis can influence the capacity of the host to respond to new infections by leading to substantial and long-lasting changes in the available CD8+ T cell repertoire (25). Taken together, these results suggest that on one hand, both CD4+ and CD8+ T cells, which are components of the acquired immune response, may actively involve in the pathogenesis of sepsis, on the other hand, the process of sepsis at different stages may also influence the counts and activities of T cells.

CD4+ T cell dysfunction is a key component of sepsis (26). In septic patients from thermal injury, immunosuppression is related to functional derangements in intestinal CD4+ T lymphocytes as represented by reduced proliferation and IL-2 production of intestinal CD4+ T cells, and a substantial apoptosis of the mesenteric lymph node (MLN) CD4+ T cells, which significantly contribute to the immunosuppression and increased susceptibility to pathogens infection in septic patient (27). Resultantly, a deregulated host response may lead to severe sepsis and contribute to mortality of patients (28). A recent study suggests that increased surface expression of a co-inhibitory immune receptor carcinoembryonic antigen-

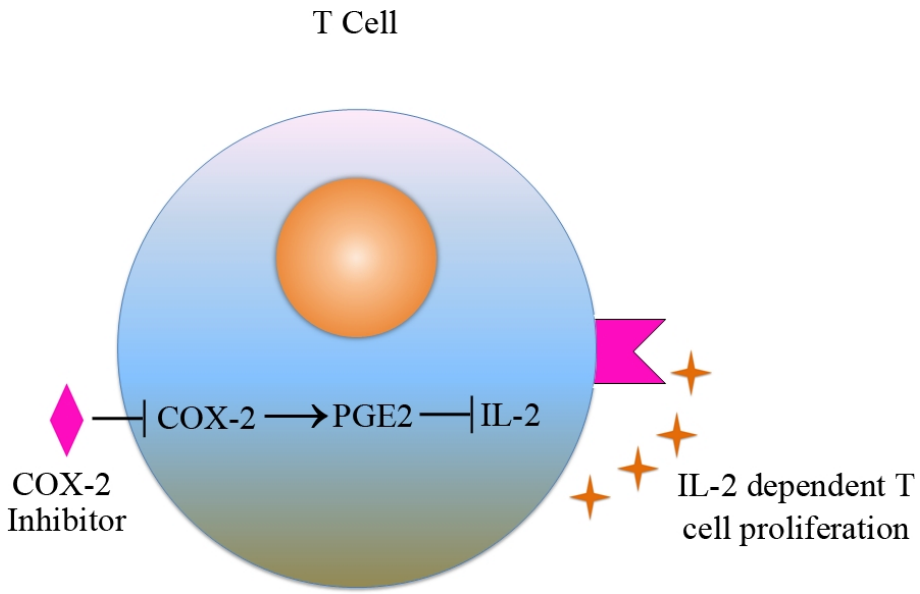

Figure 2. Prostaglandin E2 (PGE2) switchs on T cell immune response. PGE2 down-regulates IL-2 production and inhibits the growth of T cell lymphocytes, which is reversed a COX-2 inhibitor (name?). Moreover, COX-2 inhibitor prevents the decrease of ConA-mediated T-cell $[Ca^{2+}](i)$ response.

related cell-adhesion molecule 1 (CEACAM1) on CD4+ T cell and elevated level of circulating soluble CEACAM1 may contribute to sepsis-associated immune suppression (29). Moreover, it is reported that impaired CD4+ T cell proliferation and effector function correlates with repressive histone methylation events in a murine model of severe sepsis (30). Notably, CD4+ T cell activation has been shown to be necessary for neutrophil oxidative burst and phagocytosis in a septic imurine model (31). Significantly impaired CD4+ T cell activation leads to dysfunctional neutrophils, and subsequently, decreased bacteria clearance and survival, whereas excessive CD4+ T cell activation produces an activated neutrophil phenotype that leads to efficient bacterial clearance but also increased risk of tissue damage and mortality (31). Conversely, T cell activation and differentiation can also be affected by other immune cells. For instance, Delano *et al*. reported that MyD88-dependent expansion of an immature GR-1(+)CD11b(+) population induced T cell suppression and Th2 polarization during polymicrobial sepsis (32).

Regulatory T cells (Tregs) have anti-inflammatory and immunomodulatory effects, therefore play an essential role in maintaining immune tolerance, preventing sustained tissue damage and autoimmune diseases. However, Tregs may play an important role in the pathogenesis of sepsis and associated mortality. For example, a recent study showed that frequencies of Tregs were elevated in patients suffered from major burns. Moreover, higher frequencies of Tregs were detected in septic patients than those without sepsis. Among septic patients, the expressions of Tregs phenotypes and signature cytokines were markedly lower in the survival group than those in patients with fatal outcome (33). In an experimental septic imurine model, mice surviving cecal ligation and puncture (CLP) showed a markedly increased frequency of Tregs in the thymus and spleen, which was associated with reduced proliferation of CD4+ T cells. Remarkably, treatment of mice with an antibody against glucocorticoid-induced tumor necrosis factor receptor decreased frequency of Tregs, restored CD4+ T cell proliferation, reduced the levels of bacteria in spleen, and markedly improved survival of mice upon *L. pneumophila* infection. The data suggest that Tregs play a pathogenic role in the progression and establishment of a long-term immune dysfunction in septic mice (34). For targeting Tregs to alleviate the immune dysfunction in sepsis, Zhang *et al*. showed that simvastatin treatment abolished CLP-induced increase of Tregs in mice subjected to abdominal sepsis (35). Hasan *et al*. also found that CLP-evoked induction of Tregs in the spleen was reversed by inhibiting Rho kinase (36).

IL-7 is a pluripotent cytokine produced by bone marrow and thymic stromal cells that is required for maintenance of T-cell survival (37-42). IL-7 induces proliferation of naive and memory T cells (37,40,43), potentially supporting the replenishment of the peripheral T-cell pool that is severely depleted during sepsis (44,45). Multiple studies have shown the protective roles of IL-7 in the pathogenesis of sepsis. IL-7 restored immunity and decreased mortality in a viral model of lymphocytic choriomeningitis (46). IL-7 improved survival in a polymicrobial peritonitis model of sepsis (47). The cytokine also ameliorated immune dysfunction and improved survival in a model of fungal sepsis (48). IL-7 promoted T cell viability, trafficking, and functionality and improved survival in sepsis (49). Furthermore, IL-7 mediated the cross talk between Th1 and Th17 lymphocytes, which accelerated subsequent neutrophil recruitment and bacterial clearance in a murine model of sepsis (50). Thus, targeting IL-7 mediated signaling

pathway represents a promising approach to restore effective adaptive and innate immune response, improve the immune dysfunction and ameliorate the severity of sepsis.

5. CONCLUSION

The pathogenesis of sepsis is often accompanied by the dysfunction of the innate and acquired immune responses. Deregulation of T cell-mediated immunity is a consequence of immune imbalance during the process of sepsis, which subsequently affect the immune response against various infections. Deregulation of CD8+ and CD4+ T cell are key components of immune dysfunction in sepsis. CD4+CD25+Foxp3+ Tregs play an important pathogenic role in sepsis. Multiple studies have shown the protective roles of IL-7 in restoring the adaptive and innate immunity in sepsis. Therefore, targeting T cells, especially Tregs and IL-7 mediated signaling pathway may represent promising strategies for immunotherapy of sepsis.

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Abbreviations: TCR, T cell receptor; TLRs, Toll-like receptors; Tim-3, T cell Ig and mucin domain protein 3; GM-CSF, granulocyte macrophage colony-stimulating factor; DC, dendritic cells; iNOS, inducible NO synthase; NO, nitric oxide; iNKTs, invariant natural killer T cells; PGs, Prostaglandins; AA, arachidonic acid; PGE2, prostaglandin E2; Treg, Regulatory T cells

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Send correspondence to: Chen Jianghua, Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Qinchun Road 79#, Hangzhou 310003, P.R.China, Tel: 86-571-87236992, Fax: 86-571-87236992, E-mail: chenjianghua_zju@yeah.net