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SHORT REVIEW

The Importance of Detecting Regulatory T Cells in Neonatal Sepsis

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Abstract

Sepsis is a deadly complication of pediatric infection. Tregs are a typical subset of lymphocytes showing immune suppressive function. Tregs show grateful influence to immune system in neonatal sepsis. The proportion of Tregs relate with inflammatory response, Oxidative stress sepsis and this would be a new curing targeting to immunotherapy. In this short review, we analysis the research findings of Tregs in neonatal sepsis and emphasize the significance of Tregs.

Introduction

Sepsis is a common critical illness in PICU (pediatric intensive care unit) for neonates are highly susceptible to infections of bacteria, fungus and virus [1]. Detecting Tregs is significant for neonatal sepsis, regulating Treg would important target for therapy [2]. In this short review, we analysis the research findings of Tregs in neonatal sepsis and emphasize the significance of Tregs [3,4].

Regulatory T Cell

Regulatory cells (Tregs) are a subset of T cells that control autoimmune reactivity *in vivo*. They are also known as inhibitory T cells in the early stage. According to source, specificity and effector mechanism regulatory T cells can be divided into natural regulatory T (Natura I regulatory T cell) and acquired regulatory T cells (Adaptive regulatory T cell) two categories; according to this definition, CD4 + CD25 + Tregs should belong to the former, and Thl and Th3 belong to the latter. In addition to the above regulatory T cells, other Tregs have been discovered in recent years, such as: CD4 + Vβ14 + Tregs, CD8 + Tregs, CD8 + CD28 - Tregs, CD4 - CD8 - TCRαβ + (DN)Tregs, γδTregs and NKT, etc. [5,6]. Incompetence can be defined as the fact that T cells do not proliferate under the stimulation of antigen and do not produce IL-2. Incompetence of T cells mediates immunosuppression. Inhibition refers to an active, immunomodulatory process that is mediated by regulatory T cells and that can be adoptively transferred. A large amount of research evidence indicates: Incompetence [7]. These cells and Tregs are the same cells at different stages of differentiation, that is, the incompetent cells are precursor cells of Tregs.

CD4 + CD25 + CD127- Treg is the most important group. These Tregs are a typical subset of lymphocytes showing immune suppressive function, which selectively expressing molecular mark like CD25 (IL-2 receptor a), FOXP3, CTL4 (Cytotoxic T - Lymphocyte Antigen 4), LAE3 (Lymphocyte activating factor 3), TNFR (tumor necrosis factor receptor) and chemokine receptor 4,6,7,8,10. FOXP3 is specific marker of Tregs [8,9]. FOXP3 can activates the inhibiting function of CD4+ T cells which is important for differentiation and maturity of Tregs. They influence the immune balance by direct contacting with immune cells or secreting cytokines like IL-10, TGF-β [10]. They involve in various aspects of innate immune and adaptive immune like inhibiting CD4+ and CD8+ T cells functions, mediating lymphocyte differentiating from Th1 to Th2 and inducing lymphocytes apoptosis [11,12]. These Tregs also have effect on neutrophil and mononuclear macrophage to down-regulate their phagocytosis function [13]. When the host infected, the proportion of Treg will increase and results in immunosuppression [14]. The defect of Tregs will cause the severe hyperplasia of lymphoid tissue and hyperimmune activation. The important immune cells, like CD8 + and APCs (antigen presenting cell),

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will spontaneous activate and cause the inflammatory sustained damage. So Tregs are necessary in immune system [1,15].

Definition of Sepsis

Sepsis is a common complication after severe trauma, burns, and shock. In recent years, advances has been achieved in anti-infection, fluid resuscitation, wound management, and organ support treatment for severe sepsis and septic shock [16,17]. The mortality rate of sepsis remains high and is the leading cause of death in ICU patients. In 2014, the American Society of Critical Care Medicine and the European Society for Critical Care Medicine organized experts from the world of critical medicine, infectious diseases, surgery and respiratory diseases [18]. Based on the latest evidence-based medical evidence, a new definition and diagnostic criteria for sepsis, namely sepsis 3.057, was developed. The new definition states that sepsis refers to the host's dysfunctional response to infection and the development of life-threatening organ dysfunction. The new definition emphasizes organ dysfunction caused by infection and reflects more complex pathophysiological status than common infection patients [19,20].

The Immune System of Neonates

The immune system of neonates is different from adults. In fetus and neonates, the cytokines of Th2 are in the ascendant to defect the effect of Th1. INF-γ, which is a cytokine of Th1, would damage the placenta when overproduction [21,22]. The increasing proportion of Th2 is a protective mechanism to antagonize releasing INF-γ. Except that, polarization factors of Th1 and Th2 are different among neonates and adults. In neonates, the reaction of Th1 is defectiveness including the restricted production of Th1 cytokines and hypoergia of INF-γ. However, this cause the neonates immunocompromised to resist the infectious at the same time [23,24].

The Immune Dysfunction of Neonatal Sepsis

Pediatric sepsis is a systemic inflammatory response syndrome, which caused by infection. It is characterized by excessive inflammatory reaction and then the process of disease will convert to immunosuppressive state [25]. There is still no specific diagnostic criteria in clinical practice. Fever, hepatosplenomegaly, decreased white blood cell count, elevated ferritin, and elevated liver enzymes may occur when sepsis occurs. T cells play an important role in the pathogenesis of sepsis [26]. T cell-mediated neutrophils are activated after reckoning of multiple antigens by the surface of Toll-like receptors. And then neutrophils begin to recruit adaptor proteins, and rapidly activate a large number of protein kinases. Neutrophils further induce immune regulation by expressing Related gene expression, which is induced by intracellular signaling molecules, to increasing secretion of proinflammatory mediators such as IL-2, IL-6, IL-4, IL-10, and IFN-γ [27].

In the early stages of sepsis, T cell-mediated neutrophil TLR2 TLR4 expression was significantly elevated. The secretion of inflammatory mediators is increased, the immune system is activated, and harmful pathogens are effectively eliminated. However, in the later stage of the disease, the expression of TLR4 is significantly reduced, the number of T cells is decreased, and the function is significantly reduced [28]. This station causes the body to be in an immunosuppressed state. The number of T cells in the peripheral blood is reduced. On the one hand, it may be due to the large accumulation of neutrophils in the target organs, and the amount of circulating blood is insufficient. On the other hand, it may also cause apoptosis due to its killing activity, resulting in the number of T cells decrease. A large number of neutrophil apoptosis and decreased function may be one of the causes of poor prognosis in sepsis.

Imbalance between the pro-inflammatory and anti-infection in host is the key factor of the occurrence and development of pediatric sepsis. The anti-infection is often dominant in the imbalance between the pro-inflammatory and anti-infection. This leads to immunosuppression, which ultimately leads to MODS [17]. Th1 cells are characterized by the secretion of IL-2, IL-6, IFN-γ and other pro-inflammatory mediators. Th1 cells participate in cellular immunity. Th2 cells are characterized by the secretion of IL-4, IL-10 and other inflammatory mediators, regulating humoral immunity [29].

Th1 and Th2 cells are differentiated from common precursor cells. By secreting cytokines, Th1 and Th2 cells cross-regulate each other and inhibit each other to maintain balance [30]. In the initial stage of the immune response, if the body's immune system selects a subgroup-based immune response, the cells will positively boost their own superiority and inhibit another subgroup's differentiation, which results in more imbalance of Th1 and Th2 [29].

Tregs Regulate Neonatal Sepsis

Sepsis is a deadly complication of pediatric infection. When host endure the sepsis, the immune system is in a complex condition that the immune hyperfunction and immunosuppression appear at the same time [31]. By the course, immune hyperfunction and immunosuppression process a mutual competition. The results of this match decide the fate of the patient. Tregs, a kind of key Immunosuppressive cells, show grateful influence to immune system. As Table 1, we analysis some results about Tregs in neonatal sepsis [32,33].

Tregs mediate anti-inflammatory processes in proinflammatory processes, which can cause systemic inflammatory responses. The imbalance between syndrome and compensatory anti-inflammatory response syndrome affects the homeostasis and causes target organ damage.

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Table 1: Summary of research about Tregs in neonatal sepsis.

Patients	Number of cases	Detection Method	Results	Statistical Significance	Ref
Neonate	20	flow cytometry	The proportion of Tregs increase in sepsis	Yes	[51]
Neonate	100	flow cytometry	Tregs accelerate the course of sepsis	Yes	[52]
Neonate	60	flow cytometry	The proportion of Tregs increase in sepsis	No	[53]
Neonate	48	flow cytometry	The proportion of Tregs reflect the immunosuppression	Yes	[54]
Neonate	117	flow cytometry	Tregs increase the sepsis risk	Yes	[55]
Neonate	25	flow cytometry	Treg is considered as an protective mechanism to sepsis.	Yes	[56]

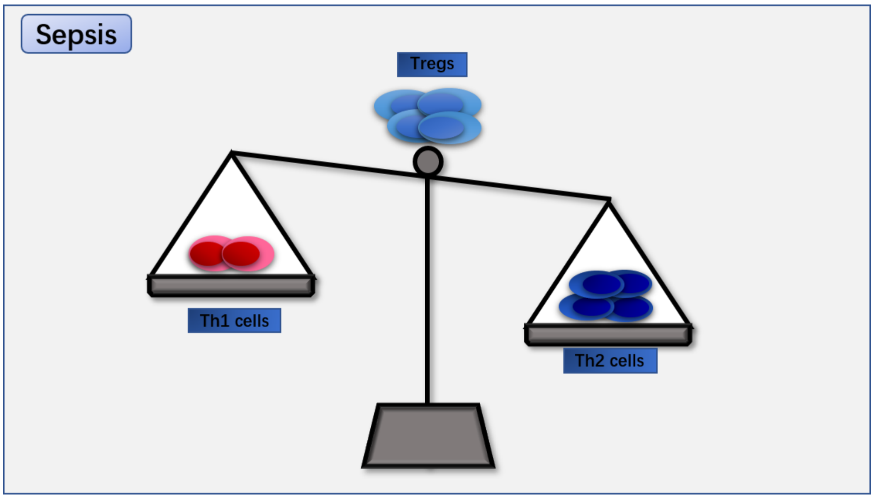

Figure 1: Tregs regulate the balance between Th1 cells and Th2 cells in sepsis.

The anti-inflammatory process mediated by Treg affects the inflammatory response and immune response to pathogens, which resulting in persistence of infection [34]. Tregs have a direct inhibitory effect on the differentiation and maturation of Th1 and Th17 cells in the CD4 + T cell subset and can also be inhibited by secreting and synthesizing various inhibitory cytokines such as TGF-β and IL-10. At Th1, Th17 cells differentiated and matured [35]. In the course of the development of a variety of inflammatory diseases and autoimmune diseases, the regulatory T cell content is abnormal, functional changes. These Tregs will cause the disordered immune response process and develop sepsis, which is closely related with the persistence of the infected lesions, and the sustained activation of the inflammatory response [36].

The course of this disease including early immune activation stage and lately immune suppression stage. In the anti-inflammatory stage, Th1 cells activate to against the invasion, which is the key point of curing neonatal sepsis and keep the patients stay alive [37]. However, the Tregs cell also be activated to differentiate when recognize the pathogene [38]. For neonates patients, Tregs have the deadly immune suppression effect that inhibit regain the Th1 cell function and turn the patient into Immune paralysis station. In the lately stage, the Tregs invalidate the APC cells and inhibit the effective immune cells activation [39]. Tregs also make the balance partial to Th2 cells and assistant with Th2 to resistant activation of Th1 (Figure 1). Th17 cells, an important proinflammatory cells, will also increase in Neonatal Sepsis. Th17 cells can release proinflammatory cytokines and activate innate immune cells to promote inflammation. The balance between Th17 and Tregs regulates the immune system. The number of Tregs is negative relative with immunoglobulin including IgA, IgM, IgG [5]. The increase of Tregs can inhibit the humoral immunity. The increase of Tregs is positive with increase of NO (Nitric Oxide), MDA (malondialdehyde) and negative with SOD (superoxide dismutase). The high expression of Tregs enhance the oxidative stress. The proportion of Tregs relate with inflammatory response, Oxidative stress reaction and humoral immunity. The skyrocket-increase of Tregs can be considered as an easy indicator to judge the condition of children [13,40].

TLRS (Toll-like receptors), a receptor of PAMPs (Pathogen Associated Molecular Patterns), is considered as a bridge of innate and adaptive immune system [41]. TLRS can recognize the endogenic and exogenous PAMPs and induce the release of signaling molecule to engage in the inflammatory response. TLRS is also considered as regulator of Tregs' function by influencing expression of FOXP3 [3]. TLR2 and TLR4 are two important receptors. TLR4 expressed on monocytes can only identify GNB (Gram-negative bacteria) and LPS. TLR4 can induce the

Th1 activation [37]. TLR2 can recognize GNB (Gram-positive bacteria), mycoplasma and yeast and induce the Th2 activation which increase the number of Tregs. Regulating TLRS can adjust the Tregs activation to accommodate the immune station [1,42].

Prognostic and Therapeutic Importance of Treg in Sepsis

Regulatory T cells are involved in the body's immune response to almost all pathogens [36]. The infection activates regulatory T cells in the pathology of sepsis. Reducing regulatory T cells will facilitate pathogen clearance and enhance defense against pathogens. However, with tissue damage and loss of immunity to reinfection, ineffective clearance of other persistent pathogens lead to more serious and even fatal immunopathological reactions [43]. The increase of Treg is accompanied by inhibiting of effective immune response and down-regulating elimination pathogen function, which may lead to fatality infection. Therefore, removal of natural Tregs or Treg-activation-related molecules including CIIA-4, TGF-β, IL-10 and G1TR will effectively regulate the inflammatory response process. Inducing or activating natural Tregs is an effective therapeutic strategy when excessive pathological damage occurs. Although Treg cells have made some progress in the prevention and treatment of clinical diseases such as vaccine preparation, how to achieve the maintenance of accompanying immunity and avoiding the balance between pathological damage, maximizing and utilizing its beneficial effects is the biggest challenge currently facing [44].

It has been elucidated that antigen presenting cells play a key role in T cell responses. Antigen presenting cells can fine regulate effector T cells by affecting the activity of Tregs to ultimately modulating immune responses [45]. Thus, any physical/chemical and biological factors that influence the development, maturation, and activation of antigen presenting cells and Tregs can affect the direction of the Th1/Th2 response to some extent, leading inflammation to different outcomes. It is also the current focus of inflammatory diseases and interventions of sepsis. Despite the different methods interventions and of application, Treg has made some progress in the application of sepsis. For example, endotoxin-stimulated mature dendritic cells are the most potent cells which can activate incapable CD4 + CD25 + Treg to stimulate proliferation and produce IL-2. In acute lethal infections, adoptive transfer of IL-10 transgenic Dyed dendritic cells can significantly reduce mortality [46].

Since Tregactivation is significantly enhanced during the pathological process of sepsis, inducting Treg apoptosis and down-regulating Treg inhibitory activity is the new clues for the treatment of sepsis. Preliminary data show that endotoxin stimulation can significantly up-regulate the inhibitory function of rat Treg on effector T cells [47]. Xuebijing, an effective traditional Chinese herb prescription, can effectively improve the inhibitory effect on T lymphocytes by promoting Treg apoptosis. In the model of sepsis caused by severe abdominal infection, after treatment with Xuebijing injection [48]. The apoptotic rate of Treg was significantly increased, and its immunosuppressive function was significantly down-regulated, suggesting that Xuebijing injection can promote the apoptosis of Treg, thus effectively improving the immune response of T lymphocytes in septic animals [49,50].

Discussion

Through the mechanism of Tregs regulating the immune system may not be conclusive. Many other factors like the pathogen species, the inflammatory state and the infection site will impact the disease. But Tregs truly involve in the innate and adaptive immune response. Detecting the proportion of Tregs is crucial to assess the immune suppressive state. Regulating Tregs can recover the immunologic balance of neonatal sepsis. So, detecting Tregs is an important factor when curing neonatal sepsis and this would be a new curing targeting to immunotherapy.

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