Proceedings of the International Conference on Modern Medicine and Global Health (ICMMGH 2023)
DOI: 10.54254/2753-8818/6/20230223

T-cells' roles and potentials as a therapeutic target in human sepsis

Muqing Zhang

Krieger School of Arts and Sciences, Johns Hopkins University, Baltimore, MD, USA

mzhan142@jhu.edu

Abstract. Sepsis is a severe syndrome that is associated with both inflammatory responses and immune system dysfunctions. The most frequent location of injuries caused by sepsis is the respiratory system, followed by the digestive system, and the circulatory system. Researchers have revealed the relationship between T cells and sepsis. To be specific, during the pathology of sepsis, T cells could be damaged, deactivated, and inhibited, while they could also act as an agent that amplifies the sepsis syndrome. This paper focuses on analyzing 3 types of T cells: CD4+ T cells, CD8+ T cells, and regulatory T cells. The populations of the first two types would be reduced, while the functions of regulatory T cells could lead to further immunosuppression during sepsis. Although to date there is no effective treatment to cure this disease, treatment plans targeting immune stimulation and Treg suppression are also examined and analyzed in depth in this paper.

Keywords: sepsis syndrome, cytokine, immunotherapy, T-cells.

1. Introduction

As a syndrome that describes the grievous inflammatory response of the human body to microbial infection, sepsis has diversified symptoms, and in its severe forms, sepsis can lead to dysfunctions of kidneys, lungs, heart, and liver, and could ultimately lead to patients' death [1-2].

1.1. Definition & diagnosis

Studies have shown that the sources of sepsis in the human body were heterogeneous. By the newest definition provided by the ESICM, sepsis can be understood as a combination of SIRS syndrome and microbial infection. The standard that is used to diagnose "SIRS" include: 1) Body temperature is out of the 36~38°C range; 2) The heart rate goes above 90bpm; 3) The respiratory rate higher than 20 breaths per minute or arterial carbon dioxide pressure goes below 32 mm Hg; 4) White blood cell count larger than 12,000,000,000 per liter or lower than 4,000,000,000 per liter [3]. If two of the four statements above occur in the body of a human individual, the individual can be diagnosed as "SIRS". Gotts and Matthay investigated the infectious causes of sepsis using the data provided by EPIC II and concluded that of the 7,000 patients classified as sepsis, 64% were detected with infections in the lungs, 20% were detected with infections in the abdomen, 15% were detected with infections in the bloodstream, and 14% were detected with infections in the renal or genitourinary tract. One universal infection site was the lungs, and the cause of high septic shock rates and the mortality rate was the combination of cirrhosis together with infection (mostly abdominal) [4].

DOI: 10.54254/2753-8818/6/20230223

1.2. Pathology

One positive fact is that the pathogenesis of sepsis has been comprehensively investigated and understood. After the human body was infected, PAMPs and DMAPs would together trigger the production of cytokines that can lead to proinflammatory responses (such as TNF-alpha). These cytokines would then trigger a series of responses, including the increase of the innate immune cell numbers, the generation of excess adhesion molecules by endothelial cells, the activation of neutrophils and NETs, and the activation of leukocytes. These responses, when surpassed a threshold, would cause systemic injuries to the human body, including increased endothelial permeability, immunothrombosis that could result in impaired microvascular function, and the reactive oxygen species damage to mitochondrial functions. The mitochondrial damage would next cause the drop in ATP levels in cells body-wide. Lacking the energy supply, the cells would be incapable of performing their functions, therefore the subsequent dysfunctions of organs would occur. Meanwhile, the increased endothelial permeability could lead to the breakdown of endothelial and epithelial barriers in lungs, kidneys, and guts, causing edema-fluid accumulation, acute kidney injuries, and bacterial translocation [4].

1.3. T-Cells and sepsis

Sepsis is a disease of the host's dysregulation of the responses to infections. As the cells which are in charge of fighting infections, the immune cells largely participate in the sepsis syndrome [5]. Among them, T cells have received a mass of attention in various sepsis researches. In this article, the roles of three kinds of T cells in sepsis will be analyzed: the ones with CD4+ glycoprotein, the ones with CD8+ glycoprotein, and the regulatory T cells. The CD4+ cells bind with the class II MHC molecule of the antigen-presenting cells, and duplicate themselves while secreting cytokines. The result of this is that the activity of other immune cells would be triggered (like B cells). The cytotoxic T cells are capable of using toxic proteins to eliminate the infected somatic cells. The regulatory T cells, as they are called, can help to regulate the immune system's functions within a moderate range, preventing the response to self-antigens [6].

1.4. Plans of treatments of sepsis

So far, there are no effective molecular therapies for sepsis. One reason is that sepsis is a very complex immune response that can lead to multiple organ dysregulations [1, 4]. It was so complex that the pathways that induce and inhibit inflammation can both be triggered simultaneously during a sepsis syndrome [7]. As a result, the development of a single treatment against sepsis is difficult. However, there are supportive treatments involving T cells that were proven to be effective in controlling the sepsis syndrome, which would be analyzed later in this article. In addition, it would be critical to investigate possible ways of curing the sepsis. This article intends to propose new ideas of possible ways for designing treatments of sepsis inferenced from the properties of T cells and the existing treatment plans.

2. Analysis I: CD4+ cells and sepsis

CD4+ T cells, with the accessory CD4 protein on their surfaces, can bind to the Class II MHC molecules. Many researches have been done to investigate the correlations between CD4+ cells and sepsis. The CD4+ T cells fit into the "helper T cells," which is one major category of the T cell family.

As previously mentioned, both excessive immune responses (including inflammation) and immunosuppression could happen during the sepsis syndrome. The excess amount of CD4+ T cells would cause the excess neutrophils to be subsequently created. As a result, the superabundant neutrophils could harm the body tissues and organs before they cleared the bacteria infectious in the human body [8]. Additionally, in an analysis of sepsis patients with burn injury, the researchers found that the proliferation of CD4+ cells and IL-2 production in the guts were both suppressed. Resultantly, the cellular apoptosis of the CD4+ helper T cells will be induced. Together, these factors would facilitate immunosuppression, causing the patients to be more vulnerable to infections [9].

The CD4+ T cells are not only the factor that can contribute to sepsis-related symptoms in human bodies, but also the victim of the sepsis. Solid pieces of evidence were found that CD4+ T cells would

DOI: 10.54254/2753-8818/6/20230223

undergo functional damages after the sepsis. For instance, after the sepsis syndrome, the ability of CD4+ T cells to generate cytokines, including many important ones like TNF-alpha, was proven to decrease [7]. The defects in cytokine secretion could further lead to the damages to the immune system functions. For another example, CD4+ T cells obtained from the patients who recovered from the sepsis syndrome revealed that the number of inhibitory receptors like PD-1 (16% higher on day 3) expressed was significantly higher than the normal cell, which would affect the strength of future immune responses [10].

Intriguingly, Chen et. al found that CD4+ T cells can be used as a prognostic indicator that can predict the occurrence of sepsis in patients. To be specific, there were more CD4+ T cells observed in survivors of the sepsis compared to the non-survivors group, with a P value of 0.046 [11]. Low levels of CD4+ T cells within patients' bodies could foreshadow severe symptoms of sepsis. Chen et. al also revealed that compared with survivors, the number of CD4+-T-cell-accompanied PD-1 receptors from the patients of the non-survivors group was observed to be higher than in the group of patients who survived, which further explained Huang et al team's results, that sepsis will result in overexpression of PD-1 receptors, and in extreme cases, the death of the patient.

3. Analysis II: CD8+ cells and sepsis

Sepsis is often associated with immune system dysfunction and abnormality in the human body. CD8+ cells are crucial components of the immune system. The exhaustion, suppression, deactivation, and damage of the CD8+ T cells can contribute to sepsis developments in human bodies.

To begin with, Lei Yan et al. measured the level of CD8+ cells in a group of 62 ARDS patients, a syndrome that was induced by sepsis. The result of the survivors' group was 254.90*10^6/L, which was more than twice the result of the non-survivors group (106.00*10^6/L). They concluded that CD8+ exhaustion could be a promising prognostic indicator for sepsis-induced ARDS [12]. The drop in the level of cytotoxic T cells would make the human body to be incapable of eliminating the infected somatic cells timely, which is a factor of immunosuppression. Another research group investigated the suppression of CD8+ cells caused by the platelets during the sepsis. They first showed that platelets would attach with CD8+ T cells through Class I MHC during the sepsis. Then they used genetic strategies to knock out the B2M gene, which encodes for a protein that is essential to form the Class I MHC. In this way, the researchers created two groups of mice: the B2m+/+ group with B2M-positive mice and the B2Mf/f-Pf4Cre group with B2M-negative mice. By the observations, the amount of CD8+ T cells of the B2M+/+ group decreased significantly after the sepsis, while the CD8+ T cell numbers of the mice of the B2Mf/f-Pf4 group didn't have the statistically significant change [13]. It can be indicated that the suppression of cytotoxic T cells could be caused by subsequent mechanisms and pathways generated by Class I MHC reacting with CD8+ T cells.

Additionally, researches investigating the impaired and deactivated CD8+ T cells were also conducted. Danahy et al. investigated the correlation between sepsis, CD8+ T cells' apoptosis, and damages of the naïve T cell precursors. From the previous analysis, it was a known fact that sepsis could lead to the decrease of CD8+ T cells in numbers through mechanisms like cellular apoptosis. Their research results were consistent with this fact as well. What's more, they experimented on the effects of sepsis on the naïve T cell precursors. They discovered that sepsis can not only reduce the numbers of these naïve T cells – it can also cause changes in the naïve CD8+ T cells' repertoire [14]. This could negatively impact the functions of CD8+ T cells in inhibiting infections, both during the ongoing sepsis and future new infections. Another team of researchers, Strother et al., investigated the CD8+ deactivation induced by dendritic cells. They concluded that due to the dysfunction of dendritic cells, the major antigen-presenting cell, during the sepsis, the IL-12 failed to be sufficiently secreted and the antigen-specific CD8+ T cells could fail to be activated. Although the amount of CD8+ T cells would not change in this process, the functions of CD8+ T cells are still inhabited.

DOI: 10.54254/2753-8818/6/20230223

4. Analysis III: regulatory T-cells and sepsis

Regulatory T cells (Tregs), as a critical component of normal body immunosuppression, have been the center of many researches on the mechanisms, pathology, and treatments of the Sepsis syndrome.

There are four major pathways that regulatory T cells can regulate the immune system and lead to a reduction of its function. Firstly, Tregs can secret cytokines that can inhibit the pathways of the immune system responses (for instance, TGF-beta); secondly, regulatory T cells can initiate pathways that could lead to immune cell cytolysis; thirdly, Tregs can interfere with the metabolic activities of immune-related cells; fourthly, Tregs can control the growth and activities of the dendritic cells [15].

Nascimento et al. investigated correlations between the cytokines IL-33 & IL-10 and the immunosuppression during sepsis. They argued that IL-33 would be released as a result of the tissue damages during the sepsis. This cytokine would activate the type 2 lymphoid cells of the innate immunity. Next, the M2 cells' (macrophages) polarization will be amplified, which would in turn increase the generation and growth of IL-10. The IL-10 cytokine molecules were the direct factor that would lead to the amplification of Tregs [16]. After the demonstration of the existence of the effectiveness of the pathway above, the researchers concluded that IL-33 could be a target of the treatment for immunosuppression.

Studies also showed that the properties and status of Tregs can change over the course of the sepsis development in human bodies. Gao et al. reviewed researches on the amount (percentage) of Tregs among survivors compared with the non-survivors of sepsis at different time points. During the early stages, the ratios of Tregs to the amount of CD4+ T cells in the two groups of people were basically identical, and the absolute numbers of Tregs in the survivors' group were slightly larger than the group of patients who died. However, since day 3, the ratio of Tregs to the amount of CD4+ T cells of the survivors reduced, while both the ratio of Tregs to the amount of CD4+ T cells and the absolute numbers of Tregs in non-survivors continuously increased. In the end, the percentage of Tregs in the survivor's group was smaller than non-survivors, while the absolute number of Tregs in the survivors was higher than the non-survivors [17]. These results showed that both a relatively moderate percentage of Tregs and the abundant amount of T cells were critical to the patient's survival. The former can prevent the immunosuppression from getting worse, and the latter can boost the clearance of infections.

5. Analysis IV: existing T-cells-related treatment methods of sepsis

Sepsis can induce pro-inflammatory mechanisms, and body-wide severe inflammation symptoms were detected in many sepsis patients. As a result, initially, the researchers focused on examining the effects of anti-inflammatory treatments on sepsis, trying to inhibit the superabundant inflammation. These trials, however, didn't achieve ideal results, because sepsis is a complex syndrome that can also induce both anti-inflammatory and immunosuppression mechanisms.

From Analysis I-III it can be concluded that T cells would experience severe defects during sepsis, including damage, inactivation, and apoptosis. The dysfunction of T cells would significantly contribute to immunosuppression since they are crucial members of the human immune system. After the failure of anti-inflammatory treatments, researchers turned their focus point to another therapeutic option: immuno-stimulations. There were molecules that were proven to be effective immune system-stimulating agents.

IFN-gamma is a cytokine manufactured by the helper T cells. The function is to activate the monocyte, an antigen-presenting cell, and therefore stimulate the activity of cytotoxic T cells [7]. Clinical cases found that the immune-adjuvant treatment involving IFN-gamma has a positive association with improved immune functions. Specifically, after the IFN-gamma treatment, the relative number of CD8+ cells increased from 12.7 to 20.8. The relative expression level of HLA-DR+, a biomarker associated with antigen presentation, increased in all T cell subsets, with an average increase rate of 105.8% [18]. In terms of the delivery methods, the inhalation-related IFN-gamma treatment was proven to be effective during another disease of lung infections: pneumonia [7].

Another substance, the granulocyte-macrophage colony-stimulating factor (GM-CSF), was argued that has a potential of being a treatment method that can indirectly enhance the T cells' functions, and

DOI: 10.54254/2753-8818/6/20230223

therefore reduce the immunosuppression. GM-CSF's function is to human bone marrow's production of cells with immune functions [7]. Namely, these immune cells include neutrophils and monocytes. The latter is the antigen-presenting cell that can stimulate the activation and functions of cytotoxic T cells. Another cytokine, IL-7, also generated in bone marrow, is a critical component in the T cell's differentiation and growth. In therapeutic designs, IL-7 was found to be an effective factor that can weaken the activity of regulatory T cells, therefore releasing immunosuppression.

Speaking of immuno-stimulation trials, it would be reasonable for researchers to think of immune checkpoint inhibitors. In Analysis I it was mentioned that the amounts of PD-1 receptors within the group of patients who survived were lower than the group of patients who died from sepsis, and PD-1functions can greatly affect the strength of the immune system. Therefore, using antibodies (the immune checkpoint inhibitors) to block the immune inhibition mechanisms like PD-1 binding with ligands PDL-1 & PDL-2 could effectively preserve the population of immune T cells and release the pressure of immunosuppression [7]. The researchers also found that blocking other components of immune inhibitions, including LAG-3 and CTLA-4, was also effective in both preserving the population of immune cells and suppressing the induction of Tregs [19].

6. Discussion

Research articles reviewed in the previous sections strongly illustrated the roles of T cells in sepsis and the existing treatment plans. However, it should be noticed that there are theories, mechanisms, and conclusions drawn by those researchers which need clarity and further investigations. Firstly, Yuan et al., claimed that the acute amplified level of antigen populations and inflammatory signals during sepsis would lead to immunosuppression [10]. However, the specific mechanism of this effect was not clearly explained. The potential explanations of this association between immune signals and immunosuppression include the existence of a threshold effect, that the overwhelming immune signals would trigger a shutdown in immune responses, or the secretion of chemical molecules triggered by these signals might have downside effects on the immune system activities. Further researches should be conducted to investigate the mechanism behind the association proposed by Yuan et al. Secondly, Guo et al. analyzed the relationship between the presence of Class I MHC and the CD8+ T cells in mice from the perspective of statistical significance [13]. Further researches should be conducted to investigate the detailed pathways about how interactions of Class I MHC molecules can cause the reduction of the size of the CD8+ cell populations. Thirdly, the results of many types of research reviewed were drawn from the comparison between the survivors of the sepsis and the non-survivors of the sepsis [16-17, 20]. The sample sizes of the non-survivors group of each of these researches, however, were relatively small. Many "n" numbers of the samples of non-survivors were smaller than 30, which made the statistical conclusions drawn from the studies on these samples relatively unpersuasive. It is unethical to expect the appearance of more non-survivors, so one solution could be the sharing of raw data on the patient's physiological situations between the research teams who investigate the comparison between survivors and non-survivors of the sepsis syndrome. Consent from the patients is definitely required, and a broader collection of data can lead to more solid results and findings.

In Analysis III, one reviewed article suggested that the amplified regulatory T cells' activities can greatly contribute to immunosuppression, and therefore the regulatory T cells inhibitions can be a promising plan for drug developments of sepsis-related immunosuppression [16]. However, Vignali et al. pointed out that according to statistical results, there was little significant association between the Tregs population's sizes and mortality rates of the sepsis syndrome. Therefore, the practical value and the practical methods of using regulatory T-cell inhibitors as sepsis treatments should be carefully evaluated. To be specific, the inhibitors could be promising drugs for fighting sepsis, but their effects on patients in the life-threatening stages of sepsis might not be significant. Further researches need to be conducted to clarify which ways of using regulatory T-cell inhibitors are the most effective ones.

In addition to immuno-stimulation plans, the inflammation symptoms during the early stages of sepsis should also be proposed. Although they might not be as effective as the treatments against immunosuppression, reducing the damage of inflammation in patients is still an important step for sepsis

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treatments. In the year of 2015, Astry et al. extracted Celastrol from Chinese herbal. The particular plant was used to treat rheumatoid arthritis in traditional Chinese medical plans. The researchers found that this compound was effective in inducing the activities of regulatory T cells and thereby reducing the inflammations and tissue damages in the joints of the human body [20]. Specific mechanisms of Celastrol include increasing the level of Tregs in joints. Therefore, it can be concluded that Celastrol can be a candidate for drug development of sepsis, and it is worth further research to confirm its effects on reliving the inflammations in the early stages of sepsis. It must be stated that generally the immune system activities should be enhanced rather than regulated during sepsis, but plans that aim to control the damages brought by the regional inflammations (in this case, joints), which can reduce the patient's pain to a certain degree, should worth consideration.

7. Conclusion

After a throughout analysis, it can be concluded that human T cells play an important role in human sepsis syndrome. Different classes of T cells, however, would participate in the sepsis pathology through different mechanisms. Major T cells with CD4+ and CD8+ receptors face severe damages during sepsis. The damages include a lack of nutrients, deactivation, and apoptosis. The reductions in the amounts and activities of these T cells could trigger the malfunctions and deregulations of immune systems during the sepsis. Contrary to the normal T cells, the activity of Tregs would be amplified during sepsis, leading to a further inhibition of the immune responses. Therefore, two different goals should be met when applying treatments for sepsis. Firstly, substances like IFN-gamma and GM-CSF can cause increases in the strength of T cells, and are used as "immuno-stimulation" factors. Secondly, substances like IL-7 can weaken the activity of Tregs, releasing immunosuppression, and therefore resuming the normal immune functions. In the future, the researchers should focus on building theories that could explain the conclusions of statistical results. The research teams of clinical sepsis studies are also encouraged to collaborate by sharing the data with each other to create solid analyses. In addition, more investigations should be conducted to treat the inflammatory syndromes that occurred in many sepsis cases.

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