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Review

Mesenchymal Stem Cells in Sepsis: From Basic Research to Clinical Application

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ABSTRACT

Sepsis is a life-threatening organ dysfunction caused by a deregulated host response to infection, and is the most common cause of death in the intensive care unit. Although the pathogenesis of sepsis has made substantial progress, the current clinical treatment of sepsis is basically symptomatic treatment, including the infusion of antibiotics and catecholamine, and no effective conventional treatment has been found. The focus of research is Mesenchymal Stem Cells (MSCs). It can be a novel therapeutic tool to treat sepsis. MSCs have the characteristics of anti-inflammatory, antibacterial, anti-apoptosis, regulating immunity, and tissue and organ repair. The pre-clinical research and a few clinical phase I studies are reviewed to review the current cell therapy for sepsis. Using the characteristics of MSCs provides new ideas for the treatment of sepsis.

1. INTRODUCTION

Sepsis is a clinical syndrome caused by a deregulated host response to an infection [1]. Sepsis is still an important clinical problem in the future [2–4]. It is a common clinical emergency and the incidence rate is increasing year-by-year. It is a common and critical disease in Intensive Care Unit (ICU) [5]. Every year, millions of patients with sepsis are added around the world, with more than a quarter of the deaths. There are more and more researches on the pathophysiological mechanism of sepsis. The development of related clinical treatment improves the prognosis of sepsis, but the mortality rate is still high. There is an urgent need for new treatments [6]. After many clinical trials, it is shown that sepsis is the result of multiple factors, and should not inhibit a single inflammatory mediator. To maximize the efficacy, and based on their immunomodulatory characteristics, Mesenchymal Stem Cells (MSCs) could be a new therapeutic tool for sepsis. This report will review the latest knowledge about the efficacy of MSCs in preclinical and phase I trials. It hopes that MSCs may bring bright prospects for the treatment of sepsis.

2. SEPSIS

Sepsis is a common condition that is associated with unacceptably high mortality and, for many of those who survive, long-term morbidity [7]. The diagnostic criteria were: infection and continuous sequential organ failure score is two points or more, and a rapid sequential organ failure assessment was established for rapid diagnosis in the environment outside the ICU. When pathogens break the natural barrier of human body and enter the human body, they activate the natural immune system through the pathogen related molecular pattern, and combine with the pattern recognition receptor expressed on the surface of the natural immune system cells to trigger the inflammatory response [8]. The innate immunity and acquired immunity of the body can regulate the immune imbalance. Neutrophils, monocytes, macrophages and pathogens arrive at the site of an inflammatory reaction in large numbers, leading to tissue and vascular endothelial damage, and progress to organ failure, coagulation dysfunction and blood flow instability [9,10]. It can act on bacteria directly by secreting antimicrobial peptide, and indirectly mediate by increasing phagocytic activity of macrophages and neutrophils. MSCs could reduce the incidence of sepsis related organ failure.

3. MSCs

Mesenchymal stem cells are pluripotent stem cells that were first isolated from bone marrow. They are capable of self-renewal and have the ability to differentiate into osteocytes, chondrocytes, adipocytes, and fibroblasts. MSCs are similar in appearance to fibroblasts and can differentiate into mesenchymes. Ability of stromal and non-mesenchymal-derived tissues was first described by hematologist *A. Friedenstein* and colleagues *K. Petrakova* and others in 1968 [11–13]. MSCs can be found in almost all tissues in the body [9,14–18]. However, due to its tissue origin from

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different adult (adipose tissue, peripheral blood, bone marrow) and neonatal tissues (specific sites of placenta and umbilical cord), MSCs activity is different, which makes the comparison of research results challenging [19–22]. Because MSCs did not express major histocompatibility complex (MHC)-II and CD40, CD80, CD86, the expression of lower MHC-I. In addition, it is generally believed that adult MSCs do not express hematopoietic markers CD11, CD34, CD14 or CD45, so they cannot be detected by immune-monitoring, and will not lead to graft rejection after transplantation [18,23]. These characteristics make them a biomedical candidate for clinical treatment of sepsis.

4. MSCs IN SEPSIS

4.1. Inflammatory Regulation of MSCs

At present, we think that the occurrence and development of sepsis are dynamic, and the body is in a state of imbalance between inflammatory response and anti-inflammatory response. Severe sepsis is a disease with circulatory, cellular and metabolic abnormalities and a high risk of death [24].

In the acute and late stages of sepsis, the body can produce pro-inflammatory and anti-inflammatory factors. Studies have found that MSCs can affect the levels of inflammatory factors in the plasma, mainly including up-regulating the levels of anti-inflammatory factors, such as Interleukin-4 (IL-4), IL-1 receptor antagonist (IL-1Ra), and Prostaglandin E2 (PGE2) and Tumor Necrosis Factor-α (TNF-α)-inducing protein-6 (TSG-6) [25,26], etc., also include down-regulating the levels of pro-inflammatory factors, such as TNF-α, IL-6 [27–30], etc. The following studies confirmed. Bouglé et al. suggested that compared with Cecal Ligation and Puncture (CLP) mice treated with salt water, the mice with micro-fragmentized fat in the retroperitoneum after 2 h of CLP modeling had higher survival rate, higher plasma cytokine level at 24 h after sepsis induction, significantly lower levels of pro-inflammatory cytokines, and higher plasma levels of anti-inflammatory cytokines [IL-4, granulocyte colony stimulating factor (G-CSF)], which weakened the inflammatory response. This study is to improve the early inflammatory state and prognosis through cyclooxygenase-2-mediated mechanism [31]. In the same way, *in vivo* and *in vitro* experiments of Pedrazza et al. also confirmed that MSCs treatment can reduce the expression of cyclooxygenase-2 and Nuclear Factor Kappa B (NF-κB), inhibit the activation of mitogen-activated protein kinase (MAPK) pathway, and thus reduce the production of inflammatory cytokines [32]. Otherwise, it has been found that up regulation of Nrf2 may be related to the reduction of inflammatory cytokines and the resistance to oxidative stress induced by sepsis [33]. Studies have also shown that MSCs can reduce the tissue concentration of TNF-α, IL-6, IL-1β and IL-12 in lung, liver, intestine and bronchoalveolar fluid [27–30].

The use of MSCs Conditioned Medium (MSC-CM) led to the histopathological changes in the lung tissue of Lipopolysaccharide (LPS) induced Acute Lung Injury (ALI) mice. The levels of IL-6 and macrophage inflammatory protein-2 and the accumulation of neutrophils decreased significantly. In addition, *in vivo* and *in vitro*, MSC-CM treatment can enhance the apoptosis of bronchoalveolar lavage fluid (BALF) neutrophils and reduce the expression of anti-apoptosis molecules Bcl-xL and Mcl-1. Human MSC-CM also reduced the activity of NF-κB and MMP-9 in neutrophils of patients with Acute Respiratory Distress Syndrome (ARDS) [34].

In addition, Mei et al. used male C57BL/6 mice to make CLP model and used Human Adipose Tissue Derived Stromal Cells (hADSCs) to intervene and mechanical ventilation to mice, it can significantly reduce the level of IL-6 in BALF and the expression of TNF-α and IL-6 mRNA in lung, liver and kidney [35]. Compared with the control group, the levels of TNF-α, IL-1β and IL-6 in the myocardium of LPS-treated animals increased. The significant decrease of serum IL-1β and IL-6 levels after treatment with MSCs is related to the significant decrease of myocardial TNF-α, IL-1β and IL-6 levels [36]. Our study has similar results and found that the levels of serum inflammatory cytokines, TNF-α and IL-6 in rats after CLP surgery were significantly increased, but they were significantly decreased in rats treated with adipose derived mesenchymal stem cells (ADMSCs) [37].

However, the group of Human Embryonic-derived MSCs (hESC-MSC) pretreated with MG-132 was injected into the mouse peritoneum 6 h after LPS was injected into the mouse peritoneum to make the model, and there was no obvious phenomenon of inflammation control, so it has research potential [38]. The levels of TNF-α, MCP-1, interferon (IFN)-γ and IL-6 were significantly decreased and IL-10 was significantly increased in mice receiving Umbilical Cord-derived MSCs (UC-MSCs) 6 h after CLP [39,40]. We found that the levels of serum Soluble Tumor Necrosis Factor Receptor-1 (sTNFR1) and IL-10 in CLP-ADMSCs group were higher than those in other groups. In all groups, the level of apoptosis and edema was consistent with that of IL-6. ADMSCs secretes sTNFR1, which is most likely to improve ALI in septic rats by reducing inflammation and pulmonary edema [41].

The latest study found that IL-37 is a new member of the IL-1 family, which has five different isoforms (named as IL-37 ae). Among them, IL-37d expresses in PBMC and UC-MSC. Secondly, IL-37d is a functional cytokine, which negatively regulates the expression of pro-inflammatory cytokines in a Smad3 dependent manner. The overexpression of IL-37d significantly inhibits the production of IL-6 induced by IL-1β in A549 cells [42]. Studies have also shown that pre-treatment of MSCs with IL-1β induces an increase in the level of anti-inflammatory miR-146 contained in MSCs exosomes. TLR4 pathway plays an important role in infection response [40]. But MSCs could not affect the mRNA expression of different toll like receptors [43]. In addition, Transforming Growth Factor-β1 (TGF-β1) is an important cytokine secreted by MSCs [44]. Under sepsis conditions, MSCs overexpressing TGF-β1 can reduce the levels of pro-inflammatory cytokines and inhibit the infiltration of macrophages in tissues. Macrophages treated with MSCs overexpressing TGF-β1 can also alleviate organ damage. This will provide new hope for the treatment of sepsis.

4.2. Immune Regulation of MSCs

More and more evidence shows that MSCs play an immunomodulatory role in sepsis. In the progress of sepsis, in addition to the imbalance of inflammatory factors, the specific immunity of T- and B-lymphocytes is active, and apoptosis is increased. Studies have shown that MSCs can inhibit the activation and proliferation

of T cells [45,46]. Inhibit the differentiation of naive T cells into T helper cells 17, and prevent T helper cells 17 from secreting pro-inflammatory cytokines [47–51]. Activation of B-lymphocytes mainly depends on T-lymphocytes. Some researchers believe that the influence of MSCs on the activity of T-lymphocytes may also indirectly inhibit the function of B-lymphocytes [52]. However, some studies have shown that MSCs can enhance the survival and function of B-lymphocytes [53]. In the innate immune response of the body, a large number of neutrophils and monocyte macrophages are produced, causing damage [31,54–56]. MSCs can reduce the production of neutrophil invasive enzymes and free radicals, reduce the damage of tissues and organs, enhance the phagocytosis mediated by neutrophils, and enhance the ability of clearing bacteria.

Mesenchymal stem cells have the immunomodulatory properties of innate and adaptive immunity, and can promote the polarization of monocytes and/or macrophages from type 1 (pro-inflammatory) to type 2 (anti-inflammatory) phenotype, which is characterized by high levels of IL-10 secretion, enhanced phagocytosis and low levels of TNF-α, prevent damage to organs and tissues [25,57–59].

Prostaglandin E2 depends on the immunomodulatory effect of Adipose MSCs (ASCs) on monocytes [60–62]. Although acute immune response is beneficial to bacterial clearance, it will damage its own tissues and even cause death [63,64]. Wu et al. studied the mechanism of MSCs mediated immunoregulation through the expression of TLR4 signal, providing the first evidence *in vivo* for the relationship between MyD88-NFκB pathway and MSCs mediated immunoregulation during sepsis [40]. In wild-type MSCs, carbon monoxide (CO) pretreatment can enhance autophagy and mitochondrial phagocytosis, reduce the production of mitochondrial Reactive Oxygen Species (ROS), prevent cells from oxidative stress-induced death, reduce mouse mortality and reduce organ damage [65]. However, the apoptosis of Alveolar Macrophages (AMs) plays a pathogenic role in ALI and severe ARDS, but bone mesenchymal stem cells (BMSCs) can partially reduce the apoptosis of AMS by inhibiting Wnt/β-catenin pathway [66].

The results of Luk et al. [67] show that the immunoregulation of MSCs depends on the recognition of MSCs by monocytes. In the medium, LPS stimulation increased the expression of CD11c in macrophages, and increased the levels of TNF-α and inducible nitric oxide synthetase. In contrast, the expression of CD11c in macrophages treated with BMSCs directly decreased. Therefore, phagocytic ability of sepsis mice becomes stronger after MSCs treatment, and co-culture does not induce phagocytosis. Therefore, in the rat model of sepsis, BMSCs reduced the inflammation of lung tissue and inhibited the expression of macrophages of CD11c [68].

The extensive transfer of mitochondria from MSCs to macrophages through Tunnel Nanotubes (TNT) like structure will lead to macrophages showing more obvious phagocytic activity. Finally, by blocking the TNT formation of MSCs and inhibiting the transfer of mitochondria, the bioenergy of macrophages cannot be changed. The phagocytosis of macrophages *in vitro* and the antibacterial effect of MSCs *in vivo* cannot be affected. This study demonstrates that the transfer of mitochondria from MSC to innate immune cells leads to the enhancement of phagocytic activity, and reveals an important new mechanism of the antibacterial effect of MSCs on ARDS [69]. Progress has been made in understanding new mechanisms, including paracrine factors released by MSCs, mitochondrial transport, and the processing of exosomes and microbubbles [70,71]. MSCs can also secrete PGE2, which promotes macrophages to produce IL-10, so as to improve organ function and reduce damage [71–73]. These findings reveal the complexity of the crosstalk between MSCs and macrophages, which may be due to the specificity of the organ and the impact of the environment at the time of injury.

In addition, MSCs have innate and adaptive immunomodulatory properties. MSCs also interfere with the differentiation, maturation and function of dendritic cells, reduce their ability to induce T cell activation, and produce cytokines with higher anti-inflammatory and lower pro-inflammatory properties [74–76]. MSCs can also regulate the pro- and anti-inflammatory phenotypes of natural killer cells, which is determined by the state of natural killer cells and the surrounding environment [77].

Therefore, MSCs can regulate the levels of IL, TNF and other classic inflammatory factors in sepsis, maintain the relative stability of the immune system, and can enter the tissues and organs to further play a role.

4.3. Bacterial Burden of MSCs

Mesenchymal stem cells can mediate the clearance of bacteria in clinical sepsis model and has strong anti-microbial activity. Rabani et al. found that MSCs enhanced non-phagocytic cell oxidase-2 (NOX-2) dependent ROS production and bacterial killing in macrophages [78]. In MSCs treated mice, the clearance rate of bacteria was significantly higher, partly due to the increased phagocytic activity of host immune cells. The data showed that MSCs may play a beneficial role in experimental septicemia through paracrine mechanism [29]. Zhu et al. induced sepsis in rats by intravenous injection of *Escherichia coli* (5×10^5/rat) for 3 days. One hour after infection, the rats were treated with Human UC-MSCs (hUC-MSCs). It was found that hUC-MSCs reduced the inflow of neutrophils, increased the number and phagocytic activity of activated macrophages (CD206+) in the spleen, and increased the survival rate and bacterial clearance rate of sepsis rats [79]. The purpose of staphylococcal enterotoxin B (SEB) pretreatment is to prolong the survival interval of transplanted MSCs and induce the production of cellular protectant, anti-apoptotic and anti-inflammatory factors. This study concluded that the transplantation of SEB MSCs has an improved therapeutic effect on the live bacterial model of sepsis. The S gene expression of SEB MSCs treated mice was down regulated, while the anti-bacterial peptide and anti-inflammatory cytokines were up regulated. Increased animal survival and bacterial clearance in blood and organs [80].

4.4. Repairing Organ Injury with MSCs

In sepsis, MSCs can induce the protection of lung, kidney, heart and other organs, improve organ failure and reduce mortality [10,81–85]. Mechanical Ventilation (MV) aggravates the multiple organ damage induced by sepsis. Mei et al. treatment with hADSC can increase the survival rate of septic MV mice and reduce the organ damage of lung, liver and kidney [35].

Another study selected MSCs from different sources to treat adult male rats with albinism after LPS. It was found that the BMSCs were significantly enhanced by Nrf2 at mRNA and protein levels to treat sepsis induced liver injury [33]. Nucleotide binding and oligomerization domain like receptor 3 (NLRP3) of inflammatory bodies are involved in the occurrence of acute liver injury in septicemia. The potential mechanism of NLRP3 is not clear [86].

Xu et al. also confirmed that BMSCs could reduce lung injury, mortality and pro-inflammatory factor surge in mice [87]. But there is also a study that BMSCs infusion does not reduce the inflammatory damage of LPS induced sepsis mice [88].

Mesenchymal stem cells showed that it can protect the heart in sepsis, but the mechanism is not clear. Wang et al. showed for the first time that exocrine miR-223 plays an important role in the heart protection induced by MSCs in sepsis [89]. Menstrual-derived MSCs (MenSCs) can increase the proliferation rate and paracrine response under specific pressure. The combination of MenSCs or AMSCs and antibiotics can greatly improve the survival rate of sepsis [90–94].

5. MSCs AND CLINICAL TRIALS

At present, of the 2314 clinical trials of MSCs (excluding withdrawal and unknown state trials), 237 researches are devoted to immune system diseases, 340 researches are devoted to inflammatory diseases, of which only 30 were related to sepsis and 15 were related to septic shock (http://clinicaltrials.gov, accessed February 2020). Table 1 shows the characteristics of the included clinical related studies [95–97]. A randomized, single blind, controlled trial (NCT 02328612) started in 2014 was conducted to explore the immune and inflammatory response of allogeneic ASCs to 32 healthy subjects after intravenous injection of LPS [95]. Four treatment arms: placebo or ASCs intravenously at either 0.25×10^6, 1×10^6, or 4×10^6 cells/kg; all subjects received LPS intravenously (2 ng/kg) 1 h after the end of ASC infusion.

The results showed that ASCs was well tolerated, and high ASCs dose (4×10^6 cells/kg) increased the fever response. ASCs play an anti-inflammatory role by enhancing the release of IL-8 and nucleosome, IL-10 and TGF-β, and enhance the procoagulant effect during sepsis. However, this study did not evaluate the safety and effectiveness of MSCs in sepsis.

A single center study on the safety and feasibility of UC-MSCs in patients with severe sepsis published in 2018 (chictr.org.cn identifier ChiCTR-TRC-14005094) divided 15 patients into three groups: low (1×10^6 cells/kg), intermediate (2×10^6 cells/kg), and high (3×10^6 cells/kg) dosing cohorts [96]. The results showed that MSCs at a dose of 3×10^6 cells/kg was safe and well tolerated.

A study published in February 2018 on cellular immunotherapy for septic shock (NCT02421484) aims to conduct a dose escalation trial of septic shock MSCs to check the safety and tolerability of MSCs [97]. The results show that the infusion of freshly cultured allogenic bone marrow-derived MSCs, up to a dose of 3 million cells/kg (250 million cells), into participants with septic shock seems safe.

There are two other safety studies on MSCs, one of which is a phase I trial published in 2017 on the use of MSCs transplantation for bronchopulmonary dysplasia in preterm infants. The results of the trials show that MSCs appear to be safe [98]. A study also revealed that UC-MSCs intravenous infusion is safe in patients with chronic stable heart failure and decreased ejection fraction, and improves left ventricular function [99].

More and more studies show that MSCs is one of the promising new therapies for sepsis [96,97,100]. However, there is a series of problems such as the safety of MSCs, so it still needs a process to apply MSCs to the clinical treatment of sepsis. At present, the negative results of clinical studies mainly show that MSCs have no obvious therapeutic effect on the human body, but there is no report of adverse events after MSCs infusion, which seems to prove that these cells can be safely used for clinical administration. The existing clinical studies mainly focus on its safety and secondary outcomes, including survival rate and system endpoint, and our team will continue to focus on it.

6. LIMITATIONS OF MSCs IN CLINICAL TREATMENT OF SEPSIS

Mesenchymal stem cells is a better choice for the treatment of sepsis, but there are some limitations in clinical application. Because the development of sepsis can lead to life-threatening organ failure, it is necessary to have a group of frozen allogeneic MSCs. However, in the development of sepsis, the transportation of MSCs is relatively difficult, and the effect of freeze-thaw on the characteristics of MSCs is still unclear [101–104]. The effect of cryopreservation on the therapeutic properties of MSCs has been highly controversial [105]. Studies have found that both *in vitro* and *in vivo* cryopreservation and subsequent thawing will not impair the phenotype, immune regulation, and angiogenic capacity of this particular UC-MSCs population [104]. However, some studies have

Table 1 | The characteristics of included clinical-related studies

First author	Year	Country	Disease	MSCs type	Route	Dose	Total participants	Study period	Safety assessments
Perlee	2018	Netherlands	Sepsis	ASCs	I.V	0.25×10^6, 1×10^6, or 4×10^6 cells/kg	32	2014/11–2015/3	NA
He	2018	China	Sepsis	MSCs	I.V	1×10^6, 2×10^6, or 3×10^6 cells/kg	15	2015/2–2016/5	Safety
Mclntyre	2018	Canada	Septic shock	MSCs	I.V	0.3×10^6, 1×10^6, or 3×10^6 cells/kg	30	2013/1–2014/5	May safe

I.V, intravenous; ASCs, adipose mesenchymal stem cells; MSCs, mesenchymal stem cells; NA, not applicated.

found that the transient warming effect reduces the function and adhesion characteristics of interstitial MSCs, while the vitality after thawing is still high, and the transient temperature rise will cause the MSCs to function [106]. Therefore, before using MSCs on a large scale for clinical application, the mechanism of freeze-thaw and warming on MSCs still needs to be explored. In addition, MSCs have the same disadvantages as blood-derived drugs. Their production depends on donors. They are expensive and cannot be replicated completely. Production time and quality depend on the characteristics of the tissue and donor used. Compared with MSCs derived from adult tissues, MSCs derived from embryonic tissues have stronger proliferation ability [107]. Therefore, to standardize the preparation of MSCs, donor selection criteria should be defined for MSCs from each tissue source.

Therefore, as a new treatment method, MSCs still need to be further studied and explored, including the timing, route and dose of administration. Only after the safety and effect of MSCs are evaluated, can MSCs be effectively used in clinical treatment.

7. CONCLUSION

Mesenchymal stem cells has a broad prospect in the treatment of sepsis, which brings hope for the treatment of sepsis. In combination with several clinical trials on sepsis, no adverse events were reported after MSCs infusion, which seems to prove that these cells could be safely used for clinical administration. Different preclinical studies have shown the beneficial role of MSCs in many indications, especially in sepsis and septic shock. According to the current research results, MSCs cannot only regulate the immune response, inflammatory state, tissue repair and antibacterial effects, but also not be constrained by the theoretical rules of embryonic stem cells, so MSCs can be widely used clinically in the future. However, the comparison of the best source of MSCs, the choice of storage and transportation mode, and the choice of which source of MSCs is the most suitable for sepsis patients with different complications, the lack of clinical research and unclear treatment mechanism restrict the development of MSCs. To promote the transformation of preclinical studies of MSCs into severe patients, more standardization of MSCs production will be needed, with emphasis on culture methods and cell characterization. Finally, carefully designed clinical trials are needed to evaluate the safety and effectiveness of critical patients. To achieve effective management and dose control of MSCs, that is, the safety and effectiveness of MSCs are still the primary concern of clinical trials of sepsis treatment, and it is also a problem that we need to further study in the future.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

All the authors contributed substantially to the work presented in this article. Tongwen Sun, Junyi Sun and Xianfei Ding conceived the study. Junyi Sun and Xianfei Ding contributed to the study protocol and wrote the article. Xianfei Ding and Tongwen Sun revised the article. The Tongwen Sun had full access to all of the data and the final responsibility for the decision to submit this article for publication. All authors read and approved the final manuscript.

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