

# World Journal of *Stem Cells*

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# Current status and prospects of basic research and clinical application of mesenchymal stem cells in acute respiratory distress syndrome

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## Abstract

Acute respiratory distress syndrome (ARDS) is a common and clinically devastating disease that causes respiratory failure. Morbidity and mortality of patients in intensive care units are stubbornly high, and various complications severely affect the quality of life of survivors. The pathophysiology of ARDS includes increased alveolar-capillary membrane permeability, an influx of protein-rich pulmonary edema fluid, and surfactant dysfunction leading to severe hypoxemia. At present, the main treatment for ARDS is mechanical treatment combined with diuretics to reduce pulmonary edema, which primarily improves symptoms, but the prognosis of patients with ARDS is still very poor. Mesenchymal stem cells (MSCs) are stromal cells that possess the capacity to self-renew and also exhibit multilineage differentiation. MSCs can be isolated from a variety of tissues, such as the umbilical cord, endometrial polyps, menstrual blood, bone marrow, and adipose tissues. Studies have confirmed the critical healing and immunomodulatory properties of MSCs in the treatment of a variety of diseases. Recently, the potential of stem cells in treating ARDS has been explored *via* basic research and clinical trials. The efficacy of MSCs has been shown in a variety of *in vivo* models of ARDS, reducing bacterial pneumonia and ischemia-reperfusion

injury while promoting the repair of ventilator-induced lung injury. This article reviews the current basic research findings and clinical applications of MSCs in the treatment of ARDS in order to emphasize the clinical prospects of MSCs.

**Key Words:** Acute respiratory distress syndrome; Mesenchymal stem cells; Pulmonary edema; Inflammatory response; Tissue repair; Pulmonary fibrosis

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**Core Tip:** Acute respiratory disease syndrome (ARDS) is a common disease with high morbidity and mortality. ARDS is characterized by increased alveolar-capillary membrane permeability, influx of protein-rich pulmonary edema fluid, and surfactant dysfunction, resulting in severe hypoxemia. Mesenchymal stem cells (MSCs) have the self-renewal and multilineage differentiation properties, and their immunomodulatory abilities have been implicated in the treatment of disease. Herein, we discuss the pathophysiology of ARDS and recent research surrounding the clinical application of MSCs in the treatment of ARDS.

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## INTRODUCTION

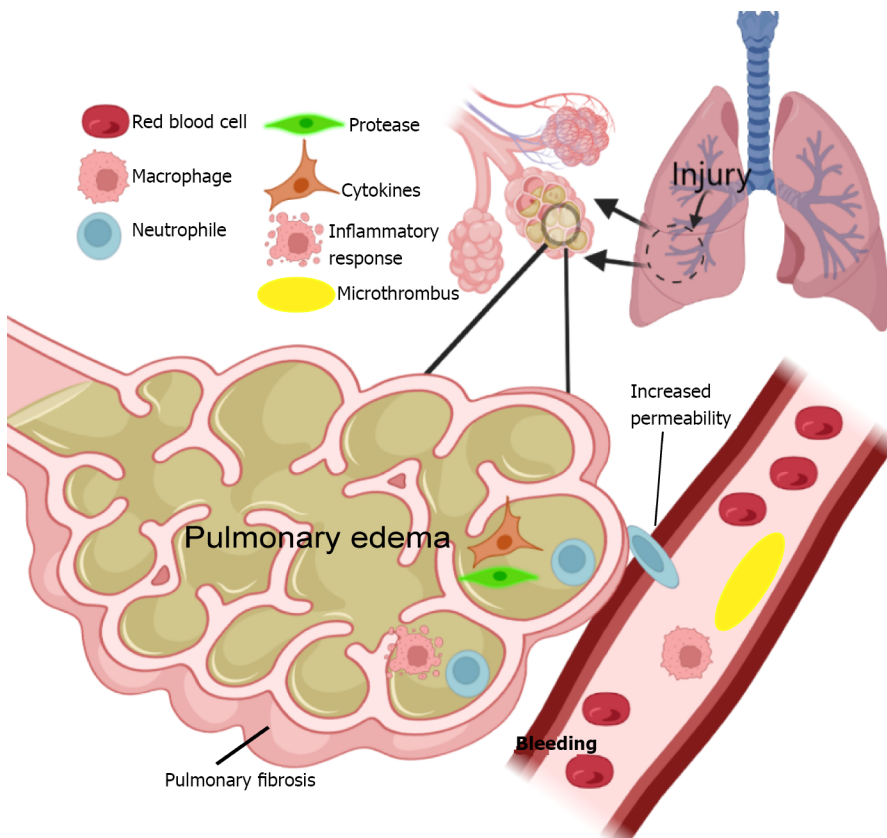
### **Acute respiratory distress syndrome**

Acute respiratory distress syndrome (ARDS) is a clinicopathological condition characterized by increased lung fluid, decreased lung compliance, and severe hypoxemia[1,2]. ARDS was defined in 1994 by the American-European Consensus Conference[3]. After several decades of research and discussions, the current internationally recognized definition of ARDS is the Berlin definition which proposes three categories of ARDS based on the severity of hypoxemia: Mild [ $200 \text{ mmHg} < \text{arterial oxygen pressure (PaO}_2\text{)}/\text{fraction of inspired oxygen (FiO}_2\text{)} < 300 \text{ mmHg}$ ], moderate ( $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 < 200 \text{ mmHg}$ ), and severe ( $\text{PaO}_2/\text{FiO}_2 < 100 \text{ mmHg}$ ), along with explicit criteria related to the timing of the syndrome's onset, the origin of edema, and chest radiograph findings[4-6]. The pathogenesis of ARDS is characterized by an unregulated inflammatory cascade with increased pulmonary endothelial and epithelial permeability[7]. Endogenous chemicals and microbial products linked to cell injury are hypothesized to attach to receptors on epithelial cells and alveolar macrophages, triggering an immunological response. The unrestricted synthesis of reactive oxygen species, leukocyte proteases, chemokines, and inflammatory substances that results to gradual lung damage. The immune-mediated reaction is known as a "cytokine storm"[8,9]. The pathophysiological changes that occur during the development of ARDS are shown in Figure 1. Currently, the clinical treatment of ARDS is rather limited and is mainly based on organ function support, such as lung protective ventilation, liver and kidney function protection, gastrointestinal function protection, venous thrombosis prevention, and nutritional support [10]. Despite the profound understanding of the molecular mechanism of ARDS, improvement of pulmonary ventilation strategies, and strengthening of supportive care for critically ill patients, the prognosis of patients with ARDS is still unsatisfactory. Currently, the global mortality rate of ARDS exceeds 40%, whilst 6%–10% of patients with respiratory failure may develop ARDS in the emergency room[11]. The long-term sequelae of ARDS include long-term cognitive impairment, psychological disease, neuromuscular weakness, pulmonary dysfunction, and decline in quality of life because of long-term medical expenses[12]. Therefore, new and safer therapies are urgently needed for ARDS treatment.

### **Mesenchymal stem cells**

Mesenchymal stem cells (MSCs) were first described by Friedenstein *et al*[13], as an adherent, fibroblast-like cell population in the bone marrow (BM) that could regenerate rudiments of bone *in vivo*[13,14]. After decades of research, it has been found that MSCs are present in a variety of tissues and organs and can also differentiate into a variety of cells to play related roles (Figure 2)[15,16]. However, the understanding of MSCs is still inadequate. MSCs were officially defined by the International Society of Cell Therapy in 2006 as follows: (1) MSCs must display plastic-adherent capacities; (2) A simultaneous





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**Figure 1** Following acute lung injury, pulmonary vascular macrophages produce chemokines to increase vascular permeability, resulting in neutrophil aggregation. Neutrophils reach the pulmonary interstitium and alveolar space and release proteases, cytokines, and other harmful substances to destroy the alveolar microstructure, leading to cell dysfunction and eventually causing exudates and lung fluid to enter the alveolar space, resulting in the development of pulmonary fibrosis. Additionally, the disorder of pulmonary vascular coagulation and fibrinolysis caused by inflammation leads to pulmonary vascular microthrombosis, which is also one of the causes of pulmonary edema.

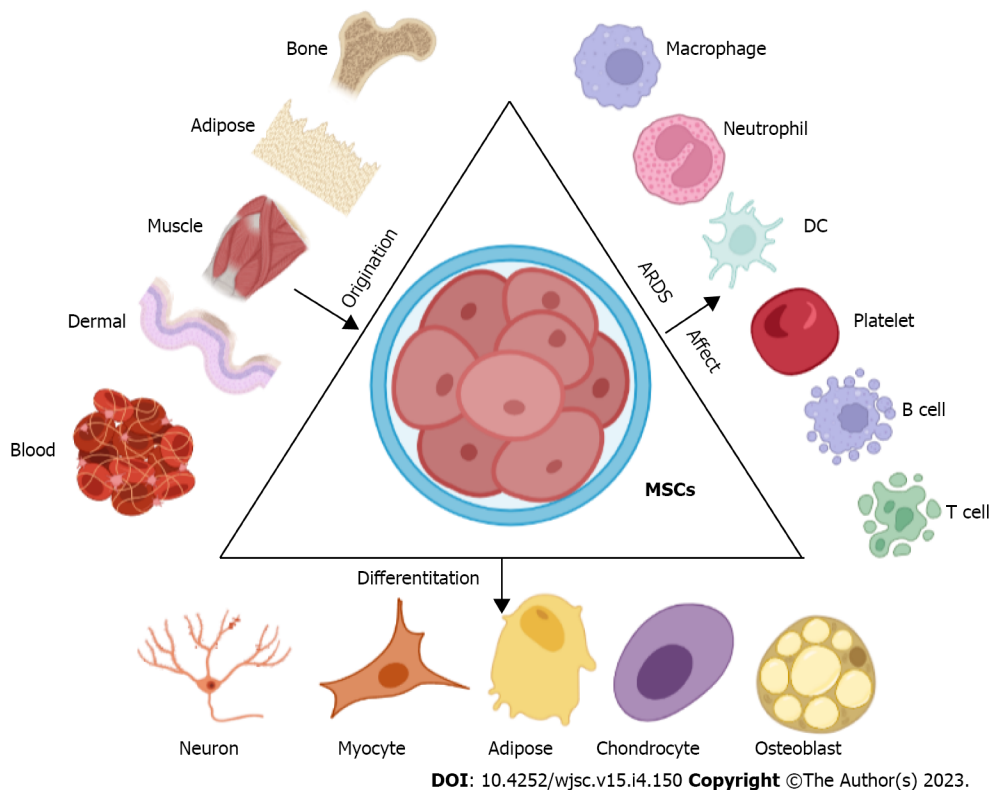
expression of stromal markers, an absence of hematopoietic or endothelial markers and human leukocyte antigen-DR surface molecules; and (3) An *in vitro* differentiation potential for osteoblasts, adipocytes, and chondroblasts[17,18]. The method of obtaining and culturing MSCs is simpler than other stem cells, and MSCs have broad application prospects in a variety of inflammatory-related diseases because of their unique immunomodulatory properties[19].

MSCs are considered a new approach for the treatment of ARDS[20]. The mechanism of MSCs in the treatment of ARDS is multifaceted, and the immunomodulatory effect of MSCs is a crucial aspect of it (Figure 3). At present, the collective view of the immune regulation ability of MSCs is based on the secretion of cytokines, such as tumor growth factor (TGF)- $\beta$  and tumor necrosis factor-stimulated gene-6 [21]. By releasing a variety of cytokines and extracellular vesicles (EVs), MSCs play anti-inflammatory and anti-cell death roles and promote the generation of microcirculation, thereby promoting the clearance of bacteria and alveolar fluid, alleviating organ damage, thus alleviating ARDS-related symptoms[22-24].

## CURRENT BASIC RESEARCH FOR THE USE OF MSCS IN ARDS TREATMENT

### Immunoregulation ability of MSCs in ARDS

The hallmark of ARDS is a series of inflammatory responses. Uncontrollable inflammatory responses are known to cause catastrophic damage to various organs[25]. MSCs are pluripotent stem cells with immune properties that can secrete a variety of cytokines, such as anti-inflammatory factors, antiapoptotic factors, and antimicrobial peptides[26-28]. MSCs regulate immune activity *via* three different mechanisms: (1) Direct contact with tissue cells; (2) Production of a series of cytokines to regulate cell activities; and (3) Exerting immune effects by regulating the activity of T cells[29-31]. Currently, the MSC treatment of ARDS is mediated by controlling inflammatory responses. Therefore, the related mechanisms have become a hot research topic, and new research findings are constantly emerging, which introduce new views.



**Figure 2 Mesenchymal stem cells can be derived from a variety of cell types and can differentiate into different types of cells to play specific roles.** In the pathological process of acute respiratory distress syndrome, mesenchymal stem cells can act on a variety of cells to play a protective role. MSC: Mesenchymal stem cell; DC: Dendritic cell.

**MSCs regulate the immune activity of the dendritic cells:** Conventional dendritic cells (cDCs) are unique antigen-presenting cells that bridge antigen immunity and innate immunity and can be activated by MSCs as regulatory DCs[32,33]. An existing study has shown that after lung injury induced by lipopolysaccharide, a large number of DCs accumulate in the lungs, which in turn aggravates lung inflammation and lung injury[34]. The underlying mechanism may involve the polarization of the T-helper cell (Th) 1 response and regulating neutrophil infiltration[35,36]. The aggregation of cDCs can lead to the activation of the Th1 pathway and aggravate the inflammatory response. At the same time, cDCs can also recruit neutrophils, prolong the life of neutrophils, upregulate innate immunity, and further intensify the inflammatory response[37,38]. MSCs also abolish the capacity of mDCs to migrate to chemokine (C-C motif) ligand 19, for DCs to display major histocompatibility complex class II peptide complexes recognized by specific antibodies, and for ovalbumin-pulsed DCs to support antigen-specific CD4+ T-cell proliferation[39].

Additionally, many studies have shown that MSC-EVs play key roles in the pathogenesis and progression of acute lung injury (ALI)/ARDS[40]. One of the underlying mechanisms may involve the potential impairment of antigen uptake, which may halt DC maturation[41]. MSC-EVs from the human BM may regulate the levels of maturation and activation markers (CD83, CD38, and CD80) and inflammatory cytokines [interleukin (IL)-6, IL-12p70, and TGF- $\beta$ ] *in vitro* via regulating the CCR7 gene by carrying miR-21-5p[42]. Additionally, the emerging role of MSC-EVs in facilitating pulmonary epithelium repair, rescuing mitochondrial dysfunction, and restoring pulmonary vascular leakage has been shown[43,44]. Therefore, regulating the maturation of DC cells in the early stage of lung injury can effectively alleviate secondary lung injury[45] (Table 1).

**MSCs induce the activation of macrophages:** Alveolar macrophages are guardians of the alveoli and airways, and interstitial macrophages are guardians of blood vessels and the lung interstitium[46]. After lung injury, tissue monocyte-derived macrophages accumulate and have increased viability in the lungs, and persist at the lesion for a long time after lung injury[47]. Macrophages respond in a variety of ways, including modulation of function (activation), the release of inflammatory chemical mediators that control immune cell recruitment, and the modulation of epithelial responses[48]. Macrophages can be divided into two phenotypes based on their functions, the M1 type in resting states and the M2 type in the activated state[49]. M1-type macrophages can secrete a variety of cytokines and participate in many processes including pro-inflammatory, pro-apoptosis, free radical formation, and matrix degradation pathways, while M2-type macrophages play a role in anti-inflammatory and anti-cell death

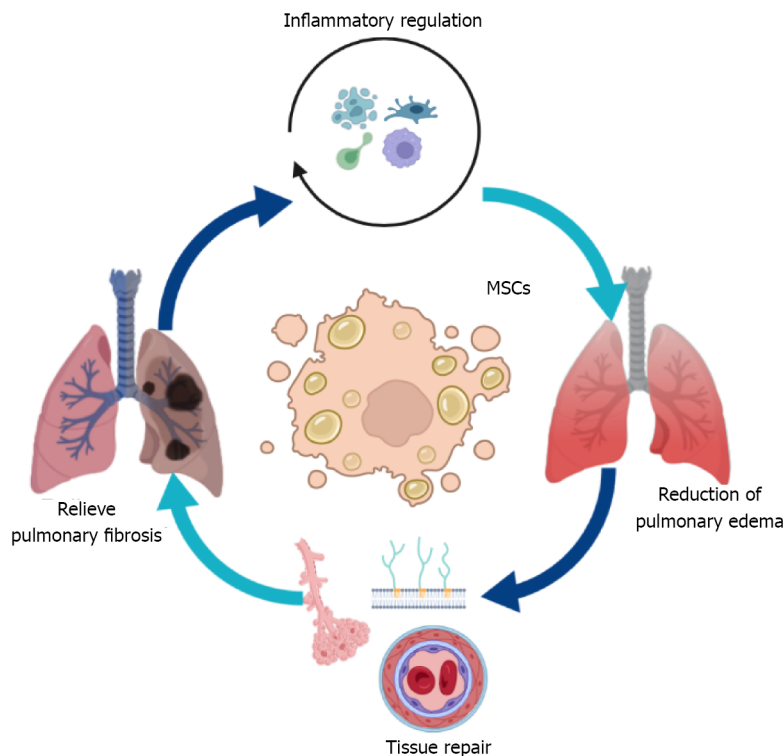


**Table 1 Recent studies on the mechanism of mesenchymal stem cell action in acute respiratory distress syndrome**

Ref.	Time	Animal/cell line	Interference	Pathway	Conclusion/main effect
Zhang <i>et al</i> [112]	2022	C-mice	Human dermal fibroblasts or MSCs were intravenously	CAP	MSC treatment significantly protects mice against bacterial pneumonia or LPS-induced lung injury <i>via</i> the CAP pathway. When the CAP was inhibited through vagotomy (VGX) and pharmacological and genetic ablation experiments, the anti-inflammatory effects of MSCs were markedly reduced in lung injury models
Kakabadze <i>et al</i> [113]	2022	Wistar rats	HPMSCs	-	HPMSCs have the ability to migrate and attach to damaged lung tissue, contributing to the resolution of pathology, restoration of function, and tissue repair in the alveolar space
Wang <i>et al</i> [114]	2022	C-mice	Human placental MSCs	Macrophage polarization pathway	Human PMSC treatment preferentially rescued resident M2 AMΦs over recruited M1 BMMΦs with overall M2 polarization to improve KP-related ARDS survival
Wang <i>et al</i> [115]	2022	SD rats	LRMSC/HMSC-C/HMSC-BM	-	Three kinds of LRMSC, HMSC-C and HMSC-BM are protective against LPS-induced lung injury, HMSC-C was more effective than LRMSC and HMSC-BM to treat LPS-induced lung injury
Zhang <i>et al</i> [116]	2022	C-mice	MSC derived microvesicles	KEGG pathway and GO function	MSV microvesicles treatment was involved in alleviated lung injury and promoting lung tissue repair by dysregulated miRNAs
Xu <i>et al</i> [60]	2022	BALB/c mice	Umbilical cord-derived MSCs	-	Transplantation of UC-MSCs transfected with SP-B could potentiate M2 macrophage polarization and further relieve LPS-stimulated lung injury
Xue <i>et al</i> [117]	2022	C-mice	Bone marrow-derived MSC	-	TGF-β1 from MSCs restored skewed Treg/Th17 levels induced by hypoxic- and LPS-stimulated conditions and reduced inflammation
He <i>et al</i> [118]	2022	Hnsccl cell line A549 (ATCC, CCL-185)	MSCs	CXCL12/CXCR4 signal axis	<i>In vivo</i> transplantation of MSCs significantly attenuated lung injury in ARDS, inhibited serum pro-inflammatory factors in mice, and down-regulated expression of apoptotic and focal factors in lung tissues
Zhang <i>et al</i> [119]	2022	C-mice	Mouse bone marrow-derived MSCs	Wnt/β-catenin transition signaling	MVs released from MSCs exerted protective effects on early fibrosis by suppressing EMT in LPS-induced ARDS
Meng <i>et al</i> [120]	2021	-	MSCs derived from normal mouse bone marrow	Akt/Mtor signaling	MTORC2 like mTORC1 as an important signaling of regulation of MSC-secreted HGF protective against LPS-induced lung endothelial dysfunction
Ishii <i>et al</i> [121]	2021	Adult male Fischer 344 rats	Adipose-derived MSCs	-	AD-MSCs enhanced the barrier function between lung epithelial cells, suggesting that both direct adhesion and indirect paracrine effects strengthened the barrier function of lung alveolar epithelium <i>in vitro</i>
Wang <i>et al</i> [122]	2021	C-mice	Bone MSCs	Vimentin-Rab7a pathway	MSCs can reach the damaged lung tissue through migration, reduce inflammatory responses and alleviate lung injury
Liu <i>et al</i> [123]	2021	SD rats	Bone marrow mesenchymal stem cell	Beclin-1	BMSC-derived exosomes were taken up by the alveolar macrophages and attenuated LPS-induced alveolar macrophage viability loss and apoptosis. Exosomes effectively improved the survival rate of ALI rats, which was associated with alleviating lung pathological changes pulmonary vascular permeability and attenuating inflammatory response

C-mice: C57BL/6 mice; CAP: Cholinergic anti-inflammatory pathway; HPMSCs: Human placental mesenchymal stem cells; PMSCs: Placental MSCs; AMΦs: Alveolar macrophage; BMMΦ: Bone marrow-recruited macrophage; Hnsccl: Human non-small cell lung cancer; KP: Klebsiella pneumonia; LRMSC: Lung resident MSC; HMSC-C: Human chorion-derived MSC; HMSC-BM: Human bone marrow derived MSC; KEGG: Kyoto encyclopedia of genes and genomes; GO: Gene ontology; SP-B: Surfactant protein B; AD-MSC: Adipose tissue-derived MSC; EMT: Epithelial-mesenchymal transition; SD: Sprague-Dawley; mTOR: Mammalian TOR; ARDS: Acute respiratory distress syndrome; ALI: Acute lung injury; TGF-β1: Tumor growth factor-β1.

processes during the inflammatory response, and promote angiogenesis and tissue repair[50-52]. The transformation of the M1/M2 phenotype helps subside the inflammatory response and alleviate tissue



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**Figure 3 The main mechanism of mesenchymal stem cell therapy for acute respiratory distress syndrome.** Mesenchymal stem cell can treat acute respiratory distress syndrome by regulating inflammatory response, reducing pulmonary edema, alleviating pulmonary fibrosis, and promoting tissue repair. MSC: Mesenchymal stem cell.

damage. In ARDS, this balance can effectively remove harmful substances and pro-inflammatory factors from the body and promote lung tissue repair. Conversely, the destruction of this balance aggravates the pathological development of ARDS. Studies have shown that MSCs can control the pathological development of ARDS by regulating the polarization of macrophages and effectively promoting the repair process in ARDS[53]. Basic studies have shown that MSC treatment reduces the expression of CD86 on macrophages in the ALI models, indicating that MSCs can inhibit the transformation of macrophages to the M1 phenotype[54]. Several mechanisms of MSCs have been described, such as: (1) MSCs can promote the phenotypic transformation of macrophages through paracrine secretion of soluble cytokines[55]; (2) MSCs promote macrophage polarization through exosomes[51]; (3) Metabolic Reprogramming[56]; (4) MSCs regulate mitochondrial transfer[57]; and (5) Apoptotic and efferocytosis effects[58]. The involved signaling pathways are as follows: (1) The nuclear factor erythroid 2-related factor 2/heme oxygenase-1 signaling pathway[59]; (2) The Notch signaling pathway; (3) The Janus kinase-signal transducer and activator of transcription signaling pathway[60]; and (4) The nuclear factor-kappa B signaling pathway[61].

**MSCs regulate the T-cell balance:** Imbalances between regulatory T cells (Tregs) and IL-17-producing Th17 are a sign of the development of inflammatory response in ARDS[62,63]. The main function of Th17 cells is to promote inflammation, release inflammatory factors, and play an important role in autoimmune diseases. Fortunately, they are precisely regulated by regulatory cells[64]. However, Treg cells can release anti-inflammatory factors (IL-4 and IL-10), control the inflammatory reaction process, and induce tissue damage repair[65,66]. Previous studies have shown that Tregs transferred into ALI animals can reduce the level of alveolar pro-inflammatory cytokines and inhibit neutrophil apoptosis and fibroblast recruitment[67,68]. A recent study also showed that a proportion of Th17 cells and Tregs > 0.79 was an independent predictor of 28-d mortality in patients with ARDS[62]. Therefore, maintaining the balance of Tregs and Th17 cells is crucial for patients with ARDS.

Existing studies indicated that, *in vitro*, MSCs repress the Th17 molecular program through the programmed cell death protein 1 pathway, prevent the differentiation of naive CD4<sup>+</sup> T cells into Th17 cells, inhibit the production of inflammatory cytokines by Th17 cells, and induce Treg phenotype[69-71]. A study has shown that TGF- $\beta$ 1, as the main paracrine cytokine of MSCs, can significantly regulate the transformation of T cells into Tregs, disturb the Th17/Treg balance, and significantly contribute to the control of inflammatory response in ARDS[72]. It is also reported that MSCs can prevent the initial differentiation of CD4<sup>+</sup> T cells into Th17 cells, inhibit the generation of inflammation, and induce the

generation of Tregs *in vitro*[73]. Several experiments have proved that controlling the level of Th17/Treg is the key to MSC-mediated control of the inflammatory response in ARDS. Therefore, it is extremely critical to find a method to regulate this balance, which may be the basis for a revolutionary breakthrough in the treatment of ARDS.

### **MSCs promote tissue repair**

Lung epithelial cell and endothelial cell damage and the exudation of highly concentrated protein fluid are the basic pathological changes in ARDS. Therefore, the treatment of ARDS requires a combination of a lung-protective ventilation strategy and fluid manipulation[74]. The immediate effect of these strategies is that MSCs can directly participate in the reconstruction of lung injury by migrating to the site of lung injury, but this aspect has less impact on ARDS injury repair[75]. Evidence shows that MSCs can be directly transformed into type II alveolar epithelial cells to support the role of injured cells[74]. Meanwhile, cell-to-cell contact also provides a prerequisite for the control of inflammatory responses [76]. The formation and tissue damage of pulmonary edema is also related to the dysfunction of the pulmonary vascular system. The increased permeability of pulmonary capillaries leads to a series of serious consequences, such as the exudation of a variety of cells and cytokines and the formation of intravascular microthrombosis. Studies have shown that MSCs can also enhance the barrier system of the pulmonary vascular system, which is beneficial for promoting the repair of lung tissue[77]. Hepatocyte growth factor, angiopoietin-1, and keratinocyte growth factor secreted by MSCs can improve vascular endothelial barrier function[78-82]. Genetic engineering *in situ* has shown that MSCs could promote the potential of pulmonary angiogenesis[83]. Therefore, various results have shown that MSCs could inhibit pulmonary edema and also provide the basis for the regeneration of lung tissue.

### **Alleviation of pulmonary fibrosis**

The cellular basis of the lung is composed of alveoli, various types of parenchymal cells, and BM-derived cells[84]. The interaction between various cells is crucial for maintaining the basic functions of the lungs[85]. Although lung protective ventilation strategies have been applied in clinical practice, ARDS survivors still have related health problems, and some patients develop fibroproliferative responses characterized by fibroblast accumulation and deposition of collagen and other extracellular matrix components in the lungs[86]. After ALI, vascular permeability increases, plasma exudates, and protein fluid aggregates, leading to pulmonary edema. Inflammatory factors from the coagulation/anticoagulation system and inflammatory system enter the lungs and damage the alveolar-capillary membrane barrier[87]. In the early inflammatory phase of ARDS, various immune cells continuously release a variety of harmful substances, including reactive oxygen species and nitrogen, as well as proteolytic enzymes such as elastase and matrix metalloproteinases, leading to lung endothelial and epithelial cell damage[86,88]. Persistent damage and failure to quickly repair this damage are the main factors that induce a pathological fibroproliferative response[89]. Late in the inflammatory response, massive and persistent accumulation of macrophages, fibroblasts, and myofibroblasts in the alveolar space results in excessive deposition of fibronectin, collagen types I and III, and other components of the extracellular matrix[90,91]. The pro-fibrotic/anti-fibrotic balance is disrupted, and the fibrogenic effect increases dramatically, leading to irreversible pulmonary fibrosis. MSCs have shown gratifying advantages in anti-fibrotic effects. In preclinical models of lung fibrosis produced by bleomycin, silica, paraquat, and radiation, MSCs obviously show the ability to prolong life time[92-95]. However, MSC control of pulmonary fibrosis is also a double-edged sword. Studies have shown that MSCs can differentiate into ATII cells *in vitro*, inhibit the production of degradation enzymes, and thereby inhibit the secretion of pro-fibrotic factors by various immune cells[96]. There is also evidence that abnormally activated Wnt/ $\beta$ -catenin and TGF- $\beta$  signaling pathways can induce the differentiation of pulmonary intrinsic MSCs into myofibroblasts and promote the development of pulmonary fibrosis [97].

## **CLINICAL EXPERIENCE USING MSCS FOR ARDS**

To date, experience with the application of MSCs in patients is limited. The data of the available clinical evidence is summarized in Table 2. Wilson and his colleagues reported the results of the phase I stem cell research for ARDS treatment (START) in 2015[98]. Patients with moderate to severe ARDS received a single intravenous dose of low [ $1 \times 10^6$  MSCs/kg predicted body weight (PBW)], medium ( $5 \times 10^6$  MSCs/kg PBW), or high ( $1 \times 10^7$  MSCs/kg PBW) ( $n = 3/\text{dose}$ ). All patients tolerated MSC infusion without prespecified infusion-related adverse events. High-dose MSCs improved daily SOFA scores compared with low-dose MSCs. Based on these promising results, the knowledge of the safety of administering MSCs to critically ill patients with ARDS is improving. A phase 2a clinical trial to evaluate the safety of BM-MSCs administered to patients with moderate to severe ARDS has also been conducted[99]. The primary outcome was safety, and secondary outcomes included respiratory, systemic, and serum biomarker endpoints. The study included 60 patients with ARDS, and intravenous Adipose-MSCs,  $1 \times 10^6/\text{kg}$  predicted body weight, *vs* the placebo was administered; however, there was

Table 2 Clinical study characteristics

Ref.	Cell type	Patient number	Outcome	Study design/evidence level	Publish time
Wilson <i>et al</i> [98]	MSC	9	No serious adverse events	Phase 1 clinical trial: A multicenter, open-label phase	2015
Matthay <i>et al</i> [99]	BM-MSCs	60	(1) No patients had any adverse events; (2) Mortality at 28 and 60 d was not significantly increased; and (3) ↑ Oxygenation index	Phase 2a safety trial: Prospective, double-blind, multicenter, randomized trial	2019
Yip <i>et al</i> [100]	UC-MSCs	9	(1) In-hospital mortality was 33.3% (3/9); (2) No serious prespecified cell infusion-associated or treatment-related adverse events; (3) ↓ Circulating inflammatory biomarkers; (4) ↓ Mesenchymal stem cell markers; and (5) ↑ Immune cell markers	Phase I clinical trial: Prospective	2020
Lanzoni <i>et al</i> [107]	UC-MSCs	24	(1) No serious adverse events; (2) ↑ Survival; and (3) ↓ Inflammatory cytokines at day 6	Phase 1/2a clinical trial: A double-blind, randomized controlled trial	2021
Dilogo <i>et al</i> [108]	UC-MSCs	20	(1) ↑ Survival; and (2) ↓ Interleukin 6	Clinical trial: A multicentered, double-blind, randomized clinical trial	2021
Monsel <i>et al</i> [109]	UC-MSCs	45	(1) PaO <sub>2</sub> /FiO <sub>2</sub> changes between D0 and D7 did not differ significantly; and (2) Clinical improvement	Clinical trial: A multicentered, double-blind, randomized clinical trial	2022
Grégoire <i>et al</i> [110]	BM-MSCs	8	(1) ↑ Survival; (2) Clinical improvement; and (3) ↓ Day-7 D-dimer value	A phase I/II Clinical Trial	2022
Kaffash Farkhad <i>et al</i> [111]	UC-MSCs	10	(1) ↑ PaO <sub>2</sub> /FiO <sub>2</sub> ; (2) ↓ Serum CRP; (3) ↓ IL-6, IFN-γ, TNF-α and IL-17 A; and (4) ↑ TGF-β, IL-1B and IL-10	Phase 1 clinical trial: A single-center, open-label	2022

UC-MSC: Umbilical cord-derived mesenchymal stem cells; CDC: Cardiosphere-derived cells; BM-MCs: Bone marrow-derived mesenchymal stem cells; PaO<sub>2</sub>/FiO<sub>2</sub>: Arterial oxygen partial pressure/fractional inspired oxygen; CRP: C-reactive protein; CT: Computed tomography; ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; TNF-α: Tumor necrosis factor-alpha; IFN-γ: Interferon-gamma; TGF-β: Tumor growth factor-β; IL: Interleukin.

no difference in the outcome in patients treated with Adipose-MSCs *vs* the placebo. In another phase I study, nine consecutive patients were enrolled, between December 2017 and August 2019, the first three patients got low-dose human umbilical cord-derived MSCs, the following three patients received an intermediate dosage, and the last three patients received a high dose[100]. The results of the first phase of clinical trials demonstrated that a single dose of human umbilical cord-derived MSCs was safe and showed good results in all nine patients with ARDS. Swedish researchers tested the systemic administration of allogeneic BM-derived MSCs ( $2 \times 10^6$  cells/kg) in two patients with severe refractory ARDS, both of whom recovered from multiple organ failure and showed reduced markers of systemic and pulmonary inflammation[101]. In summary, clinical studies report that MSC administration is safe for patients with ARDS, with few adverse reactions. However, due to the relatively small number of patients in these studies, further research is needed to test the curative effect.

## MSCS FOR CORONAVIRUS DISEASE 2019-INDUCED ARDS

Coronavirus disease 2019 (COVID-19) is an infectious disease responsible for the COVID-19 pandemic, caused by a novel coronavirus called severe acute respiratory syndrome-coronavirus 2[102,103]. COVID-19 has various respiratory and non-respiratory clinical manifestations, including mild or severe influenza-like syndrome, pneumonia, or respiratory failure, which may eventually lead to sepsis with multiple organ failure. The most common reason for being admitted to intensive care units is a respiratory failure caused by ARDS[104,105]. In a case series, Hashemian *et al*[106] found that multiple infusions of high-dose allogeneic prenatal MSCs are safe and can relieve the respiratory distress of severe patients with COVID-19 and inhibit the inflammatory response[106]. 24 participants were randomly assigned to either the umbilical cord-derived mesenchymal stem cell (UC-MSC) therapy or the control group in a double-blind, phase 1/2a randomized controlled trial. The UC-MSC treatment group got two intravenous infusions of  $100 \pm 20 \times 10^6$  UC-MSCs, while the control group received two infusions of vehicle solution[107]. The primary endpoint was safety (adverse events) after 6 h; cardiac arrest or death within 24 h post-infusion) and secondary endpoints included patient survival at 31 d after the first infusion and time to recovery. Serious adverse events related to UC-MSC infusion were

not observed. Thus, UC-MSC is safe to inject into patients with COVID-19-induced ARDS. In subjects who received UC-MSC treatment, inflammatory cytokines decreased significantly on the sixth day. In a recent clinical research, 40 COVID-19 patients who were critically unwell got either saline or intravenous UC-MSCs[108]. The findings revealed that the survival rate of patients in the UC-MSCs group was 2.5 times greater than that of the control group. Among patients with complications, the UC-MSCs group had a fourfold greater survival rate than the control group. A multicenter, double-blind, randomized, placebo-controlled trial (STROMA-CoV-2) in France, with 45 enrolled patients, has also been conducted[109]. Patients were randomly assigned to receive three intravenous infusions of  $1 \times 10^6$  UC-MSCs/kg or placebo (0.9% NaCl) over 5 d after recruitment.  $\text{PaO}_2/\text{FiO}_2$  changes between D0 and D7 did not differ significantly between the UC-MSCs and placebo groups. Six (28.6%) of the 21 UC-MSCs patients and six (25%) of the 24 placebo patients had serious adverse events not related to UC-MSCs treatment. A phase I/II clinical study was also done in patients with severe COVID-19 to assess the safety and effectiveness of three intravenous infusions of BM-derived MSCs at 3-d intervals[110]. Eight intensive care unit patients requiring supplemental oxygen were treated with BM-MSCs. Survival was significantly higher in the MSC group at 28 and 60 d, but there was no significant difference in the number of invasive ventilation-free days, high flow nasal oxygenation-free days, oxygen support-free days, or intensive care unit-free days. MSC infusion was well tolerated, and no adverse effects associated with MSC infusion were reported. Furthermore, a single-center, open-label, phase 1 clinical trial enrolled 20 confirmed COVID-19 patients with mild-to-moderate degree ARDS, who were divided into two groups: The control and the intervention group (UC-MSCs)[111]. The patients received three intravenous infusions of UC-MSCs ( $1 \times 10^6$  cells/kg BW per injection) every other day. There were no adverse effects to cell infusion throughout the clinical study, oxygenation was greatly enhanced, anti-inflammatory factor levels were significantly increased, and pro-inflammatory factor levels were dramatically lowered. This intervention may reduce cytokine storms and restore respiratory function.

To summarize, MSCs from different tissues, such as BM, adipose, UC, and placental tissues, have entered the clinical trial stage. Some studies have used MSCs to treat COVID-19-induced ARDS.

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## PROSPECT

With the progress of scientific research, our understanding of the physiological and pathological processes of ARDS has gradually deepened, and the relevant treatment methods are also improving year by year. However, the final prognosis of patients has not improved much; therefore, it is particularly important to find a method to treat ARDS. MSCs have a variety of characteristics that are striking. At present, as a potential therapeutic method, MSCs have gradually entered the international arena of research and have been unanimously recognized by scientists worldwide. Their application has achieved some effect in improving the survival rate of patients with ARDS. However, because of various reasons, only a few clinical trials are conducted. Although the achievements of basic research are emerging endlessly, there is a theoretical basis for MSC use to enter clinical treatment, and the side effects of MSCs are not clear. Moreover, their clinical application involves ethical issues. As a cell therapy, its safety needs a lot of control experiments to be proven. This has hindered the successful application of MSCs. Fortunately, the basic experimental research on their mechanism of action is becoming more and more in-depth, and the application value of MSC therapy is also much clearer. Their successful application for the treatment of ARDS is expected to improve the quality of life of patients.

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## CONCLUSION

Due to the impasse that has been reached in the treatment of ARDS, MSC therapy has gained increasing attention. MSCs are known for their anti-inflammatory, differentiation, paracrine, and microvesicle transport abilities, which could perfectly target the pathological mechanisms of ARDS, providing a theoretical basis for treatment and precision treatment. Despite the current evaluation of MSC treatment of ARDS, further research is needed to observe the specific response to MSC treatment in the long term.

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