Current understanding of the therapeutic benefits of mesenchymal stem cells in acute respiratory distress syndrome

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Abstract The acute respiratory distress syndrome (ARDS) is a multifaceted lung disorder in which no specific therapeutic intervention is able to effectively improve clinical outcomes. Despite an improved understanding of molecular mechanisms and advances in supportive care strategies, ARDS remains associated with high mortality, and survivors usually face long-term morbidity. In recent years, preclinical studies have provided mounting evidence of the potential of mesenchymal stem cell (MSC)-based therapies in lung diseases and critical illnesses. In several models of ARDS, MSCs have been demonstrated to induce anti-inflammatory and anti-apoptotic effects, improve epithelial and endothelial cell recovery, and enhance microbial and alveolar fluid clearance, thus resulting in improved lung and distal organ function and survival. Early-stage clinical trials have also demonstrated the safety of MSC administration in patients with ARDS, but further, large-scale investigations are required to assess the safety and efficacy profile of these therapies. In this review, we summarize the main mechanisms whereby MSCs have been shown to exert therapeutic effects in experimental ARDS. We also highlight questions that need to be further elucidated and barriers that must be overcome in order to efficiently translate MSC research into clinical practice.

Keywords Acute respiratory distress syndrome · Biomarkers · Cell therapy · Clinical trials · Mesenchymal stem cells · Lung · Paracrine effects

Abbreviations
Ang-1 Angiopoietin-1
ARDS Acute respiratory distress syndrome
ATP Adenosine triphosphate
ECMO Extracorporeal membrane oxygenation
ENaC Epithelial sodium channel
Introduction

The acute respiratory distress syndrome (ARDS) is a common cause of respiratory failure in critically ill patients. It is characterized by acute and refractory hypoxemia, noncardiogenic pulmonary edema, diffuse alveolar damage, and reduced compliance (or increased lung stiffness) (ARDS Definition Task Force et al. 2012) (Fig. 1). Despite advances in the understanding of ARDS pathophysiology and development of supportive care approaches, such as protective mechanical ventilation, antibiotic and fluid therapies, sedation management, prone positioning, and extracorporeal membrane oxygenation (ECMO), it remains a devastating, life-threatening disorder associated with a high mortality rate (ranging from 35 to 60% depending on underlying disease severity) (Bellani et al. 2016; Máca et al. 2017; Papazian et al. 2019). Furthermore, those patients who survive usually face long-term morbidity, which significantly impairs their quality of life (Biehl et al. 2015).

Mounting evidence suggests that cell-based therapies hold therapeutic promise for lung diseases and critical illnesses. Most experimental data have focused on the effects of mesenchymal stem cells (MSCs) from several sources, but some studies have also investigated the therapeutic actions of bone marrow-derived mononuclear cells, endothelial progenitor cells, and others (Li et al. 2013; Silva et al. 2014; Gülüner et al. 2015). As no experimental model fully reproduces the pathologic findings observed in human ARDS, a growing number of studies have investigated the efficacy of cell-based therapies across a wide spectrum of experimental models of ARDS (Table 1). Nevertheless, only three, early-stage clinical trials have been completed (Zheng et al. 2014; Wilson et al. 2015; Matthay et al. 2019) and few others are in progress to evaluate the safety of MSC therapy.

In this review, we summarize the main mechanisms by which MSCs have been demonstrated to promote therapeutic benefits in experimental ARDS and shed light on barriers that must be overcome in order to efficiently translate MSC research into clinical practice.

Mesenchymal stem cells

MSCs were initially isolated from the bone marrow and characterized as an adherent, non-phagocytic, clonogenic, and fibroblast-like cell population (Friedenstein et al. 1968). In 2006, the International Society for Cellular Therapy established minimal criteria to define MSCs: (1) they must be plastic-adherent under standard culture conditions; (2) they must express certain cell surface epitopes, such as CD73, CD90, and CD105, and lack expression of CD11b or CD14, CD34, CD45, CD79, and human leukocyte antigen (HLA)-DR; and (3) they must be able to differentiate into adipocytes, chondroblasts, and osteoblasts in vitro (Dominici et al. 2006). To date, it is known that MSCs can be obtained not only from bone marrow but also from several other tissue sources, including adipose tissue, lung tissue, umbilical cord, and menstrual blood. Furthermore, heterogeneities in gene expression and stability, secretome, and cell surface proteins have been observed in MSCs from different sources, which might impact on their immunomodulatory actions (Ostanin et al. 2011; Nora et al. 2012; Elahi et al. 2016; Heo et al. 2016; Silva et al. 2018a).

Compared to other cell populations, MSCs have demonstrated certain properties that make them more attractive candidates for therapeutic use. They have lower tumorigenic potential than embryonic stem cells and can be rapidly expanded ex vivo, which enables their clinical use in single- or multiple-dose regimens (Weiss et al. 2011). MSCs also exert immunomodulatory actions
without the need for host-recipient matching, thus allowing their use in either autologous or allogeneic transplantation. MSCs exhibit low expression of HLA type I; HLA type II exists intracellularly but is absent on the cell surface. When cells are preconditioned with interferon (IFN)-γ, HLA type II can traffic to the cell surface, but MSCs still evade recognition by alloreactive T cells (Le Blanc et al. 2003). Finally, MSCs can detect specifically injured environments and tailor their responses accordingly, which provides an advantage for their use in many diseases (Mathieu and Loboa 2012; Galleu et al. 2017; Leuning et al. 2018; de Castro et al. 2019; Islam et al. 2019).

The mechanisms by which MSCs exert their therapeutic effects are not entirely elucidated and possibly engage multiple signaling pathways. Some postulated mechanisms include cell contact-dependent actions and secretion of paracrine or endocrine factors, which act on nearby cells or travel through the blood to exert their effects. Regardless of whether by contact-dependent or contact-independent mechanisms, MSC administration has been shown to result in anti-inflammatory and anti-apoptotic effects, enhanced epithelial and endothelial cell recovery, microbial and alveolar fluid clearance, and, ultimately, reductions in multiple organ injury and mortality (Fig. 2). Notably, although many experimental studies have used vehicle (regular saline or phosphate-buffered saline) as a negative control, no therapeutic benefits were observed when fibroblasts were used as a negative control cell population, indicating that only
MSCs have the ability to induce such therapeutic benefits (McIntyre et al. 2016).

**Therapeutic benefits of MSC therapy in experimental ARDS**

**Anti-inflammatory effects**

Pathogen- and damage-associated molecular patterns trigger pro-inflammatory responses by resident epithelial and vascular endothelial cells, which results in influx of inflammatory cells and tissue injury. Administration of MSCs either intratracheally or intravenously has been demonstrated to mitigate inflammation by reducing levels of several inflammatory mediators, including interleukin (IL)-1-α, IL-1β, IL-6, IL-8, IFN-γ, macrophage inflammatory protein (MIP)-1, MIP-2, and tumor necrosis factor (TNF)-α, while also increasing levels of anti-inflammatory and pro-resolution factors, such as IL-1 receptor antagonist (IL-1RN), IL-10, prostaglandin E₂ (PGE₂), lipoxin A₄ (LXA₄), and TNF-inducible gene (TSG)-6. Such findings were observed in lung tissue homogenates, bronchoalveolar lavage fluid, plasma, and distal organs in distinct models of experimental ARDS (Table 2). A transcription network analysis also revealed that MSC administration may induce downregulation of endotoxin/toll-like receptor (TLR)-innate immune pro-inflammatory responses, while upregulating nuclear factor of activated T cell (NFAT)-related genes, which indicates a shift from innate to adaptive immune responses (dos Santos et al. 2012). Importantly, the anti-inflammatory effects of MSCs have been mostly attributed to paracrine/endocrine mechanisms, as few to no donor-derived cells localize at the host lung tissue after MSC therapy, and MSC-conditioned media has also been shown to decrease pro-inflammatory mediator levels and cell counts in many ARDS models. In this line, certain therapeutic benefits induced by MSCs have been correlated to their ability to produce extracellular vesicles (EVs), which are membrane vesicles ubiquitously secreted by cells. EVs can carry small, messenger, and other RNAs, as well as proteins, lipids, and organelles, which can alter gene

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**Table 1** Main animal models of acute respiratory distress syndrome used in MSC therapy research

| Etiology          | Model          | Disease severity* | Pulmonary features                                                                 |
|-------------------|----------------|-------------------|------------------------------------------------------------------------------------|
| Pulmonary ARDS    | Alveolar epithelium is the primary structure injured in the lungs | LPS i.t. | Mild to moderate | PMN cell infiltration in intra-alveolar areas, diffuse alveolar edema, mild changes in epithelial permeability; usually heals with few areas of fibrosis |
|                   |                | Live bacteria i.t. | Mild to severe | PMN cell infiltration in intra-alveolar areas, increased epithelial permeability, alveolar edema, protein deposition in the airspaces |
|                   |                | Hyperoxia         | Mild to moderate | PMN cell infiltration in vessels and interstitium with mild infiltration in intra-alveolar areas, presence of alveolar exudates, vascular congestion; heals with areas of scarring |
| Extrapulmonary ARDS | Vascular endothelium is the primary structure injured in the lungs | LPS i.p. or i.v. | Mild to moderate | PMN cell accumulation in capillaries and interstitium with mild infiltration in intra-alveolar areas, presence of protein-rich alveolar edema, mild changes in epithelial permeability; usually heals with few areas of fibrosis |
|                   |                | Live bacteria i.p. or i.v. | Mild to moderate | PMN cell sequestration in alveolar capillaries, interstitial edema, intravascular congestion, mild protein deposition in the airspaces, no hyaline membrane formation |
|                   |                | CLP               | Mild to severe | PMN cell accumulation in interstitial and alveolar areas, increased epithelial permeability, alveolar and interstitial edema, mild hyaline membrane formation |

*CLP, cecal ligation and puncture; *i.p.*, intraperitoneal; *i.t.*, intratracheal; *i.v.*, intravenous; LPS, lipopolysaccharide; MSC, mesenchymal stem cell; PMN, polymorphonuclear

*The severity can vary depending on animal species and injury protocol (e.g., endotoxin or inoculum dose)*
expression and modulate the behavior of target cells (Yáñez-Mó et al. 2015).

MSCs can induce upregulation of TSG-6, a potent anti-inflammatory mediator that inhibits neutrophilia by suppressing CXCL8-mediated chemotaxis (Danchuk et al. 2011; Dyer et al. 2014). In a model of zymosan-induced peritonitis, macrophage-produced TNF-α stimulated MSCs to produce TSG-6, which acted as a negative feedback loop on macrophage inflammatory signaling (Choi et al. 2011). Knockdown of TSG-6 expression in MSCs has demonstrated to abrogate several anti-inflammatory actions of MSC therapy in experimental models of endotoxin-induced lung injury (Danchuk et al. 2011). MSCs also reduced tissue injury by inhibiting formation of neutrophil extracellular traps (Pedrazza et al. 2017). Furthermore, MSC therapy can induce production of IL-1RN to protect lung tissue against bleomycin-induced injury by blocking the production and/or activity of IL-1α and TNF-α (Ortiz et al. 2007). Repeated administration of cell therapy also prevented disease progression by mitigating expression of IL-1α, IL-1β, and IL-1R1, while enhancing expression of IL-1RN, in experimental silicosis-induced lung injury (Lopes-Pacheco et al. 2013).

When exposed to endotoxin or TNF-α, MSCs increased production of PGE₂, which induced resident macrophage polarization toward the anti-inflammatory M2 phenotype and increased production of IL-10 (Németh et al. 2009). In this context, enhanced production of IL-10 has been correlated with inhibition of rolling, adhesion, and transmigration of neutrophils (Németh et al. 2009) and suppression of effector T cell
Table 2 Publications evaluating the efficacy of mesenchymal stem cell-based therapies in models of experimental acute respiratory distress syndrome

| Reference          | Injury model                     | Treatment     | Route | Regimen                          | Main findings                                                                 |
|--------------------|----------------------------------|---------------|-------|----------------------------------|-------------------------------------------------------------------------------|
| Gupta et al. 2007  | C57BL/6 mouse, LPS i.t.          | BM-MSCs       | i.t.  | $7.5 \times 10^5$ cells, 4 h after injury | ↑ survival and IL-10 level, ↓ pulmonary edema, alveolar epithelial permeability, TNF-α and MIP-2 levels |
| Ortiz et al. 2007  | C57BL/6 mouse, bleomycin         | BM-MSCs       | i.v.  | $5 \times 10^5$ cells, immediately after injury | ↑ IL-1RN levels, ↓ IL-1α and TNF-α levels                                      |
| Lee et al., 2009   | Ex vivo human perfused lung, LPS i.t. | hBM-MSCs     | i.t.  | $5 \times 10^6$ cells, 1 h after injury | ↑ alveolar fluid clearance, αENaC expression, ↓ pulmonary edema, endothelial barrier permeability |
| Németh et al. 2009 | C57BL/6 mouse, CLP               | BM-MSCs       | i.v.  | $1 \times 10^6$ cells, 24 h before or 1 h after injury | ↓ multiple organ dysfunction, vascular permeability, TNF-α and IL-6 levels, ↑ survival and IL-10 level, Reprogramming of host lung macrophages |
| Krasnodembskaya et al. 2010 | C57BL/6 mouse, E. coli i.t. | hBM-MSCs     | i.t.  | $1 \times 10^6$ cells, 4 h after injury | ↑ LL-37 level, ↓ bacteremia and MIP-2 level                                      |
| Lee et al. 2010    | Sprague-Dawley rats, bleomycin   | BM-MSCs       | i.v.  | $1 \times 10^7$ cells, 4 days after injury | ↓ lung inflammation and fibrosis, mediator levels (IL-6, IL-1β, TNF-α, VEGF, TGF-β), nitric oxide metabolites |
| Mei et al. 2010    | C57BL/6 mouse, CLP               | BM-MSCs       | i.v.  | $2.5 \times 10^5$ cells, 6 h after injury | ↑ survival, bacterial clearance, ↓ vascular permeability, mediator levels (IL-6, IL-10, JE, IL-1β, KC, CCL5) |
| Danchuk et al. 2011| BALB/c mouse, LPS o.a.           | hBM-MSCs     | o.a.  | $5 \times 10^5$ cells (divided in two doses), 4 h after injury | ↓ lung inflammation, pulmonary edema, mediator levels (IL-1α, IL-1β, IL-17, MIP-1α, MCP-1), MPO activity, ↑ TSG-6 |
| Kim et al. 2011    | ICR mouse, E. coli i.t.          | hUC-MSCs      | i.t.  | $1.5 \times 10^5$ cells, 3 h after injury | ↑ survival, ↓ lung inflammation, pulmonary edema, mediator levels (IL-1α, IL-1β, IL-6, TNF-α, MIP-2) |
| Sun et al. 2011    | BALB/c mouse, LPS i.t.           | hUC-MSCs      | i.t.  | $1 \times 10^6$ cells, 1 h after injury | ↑ survival, IL-10 levels, percentage of Foxp3+ T-reg cells, ↓ pulmonary edema, mediator levels (TNF-α, MIP-2, IFN-γ) |
| Dos Santos et al. 2012 | C57BL/6 mouse, CLP          | BM-MSCs       | i.v.  | $2.5 \times 10^5$ cells, 6 h after injury | ↓ sepsis-induced mitochondrial-related functional derangement, TLR pro-inflammatory transcriptional responses, ↑ transcriptional responses related to preservation of endothelial/vascular integrity |
| Gupta et al. 2012  | C57BL/6 mouse, E. coli i.t.      | BM-MSCs       | i.t.  | $7.5 \times 10^5$ cells, 4 h after injury | ↑ survival, bacteria clearance, lipocalin 2 levels, ↓ pulmonary edema, MIP-2, TNF-α, MPO levels |
| Li et al. 2012     | Sprague-Dawley rats, LPS i.t.    | hUC-MSCs      | i.v.  | $5 \times 10^5$ cells, 1 h after injury | ↑ survival, ↓ pulmonary edema, lung inflammation, mediator levels (TNF-α, IL-1β, IL-6), ↑ HO-1, ↓ MDA |
| Reference                          | Injury model                      | Treatment       | Route       | Regimen                        | Main findings                                                                                                                                                                                                 |
|-----------------------------------|-----------------------------------|-----------------|-------------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Krasnodembskaya et al. 2012       | C57BL/6 mouse, P. aeruginosa i.p. | hBM-MSCs        | i.v.        | $1 \times 10^6$ cells, 1 h after injury | ↑ survival, bacteria clearance, plasma C5a levels, phagocytic activity in blood monocytes                                                                                                                  |
| Zhang et al. 2012                 | Kunming mouse, hypoxenia          | BM-MSCs         | i.p.        | $1 \times 10^5$ cells, 7 days postnatal | ↑ survival, surfactant protein-C expression ↓ lung structure distortion and fibrosis                                                                                                                   |
| Curley et al. 2013                | Sprague-Dawley rats, VILI         | BM-MSCs         | i.t. or i.v.| $4 \times 10^5$ cells, ~ 3 h after initiation of VILI | ↑ IL-10 (i.v. only), KGF (i.t. only) ↓ pulmonary edema, lung inflammation and injury, TNF-α and IL-6 levels Improved arterial oxygenation and lung compliance |
| Lee et al. 2013                   | Ex vivo human perfused lung, E. coli i.t.| hBM-MSCs | i.t.        | 5–10 × 10⁶ cells, 1–2 h after injury | ↑ alveolar fluid clearance, bacterial clearance, macrophage phagocytosis capacity ↓ lung inflammation                                                                                                              |
| Maron-Gutierrez et al. 2013       | C57BL/6 mouse, LPS i.t. or i.p.  | BM-MSCs         | i.v.        | $1 \times 10^5$ cells, 24 h after injury | ↓ Est,L, alveolar collapse, lung inflammation and fibrosis ↑ MMP-8, ↓ TIMP-1 Shift in macrophage phenotype from M1 to M2                                                                                       |
| Zhao et al. 2013                   | Sprague-Dawley rat, chest impact + LPS i.v. | BM-MSCs | i.v.        | $5 \times 10^6$ cells, 2 h after LPS challenge | ↑ survival, IL-10 level ↓ lung inflammation, TNF-α and IL-6 levels                                                                                                                                                              |
| Asmussen et al. 2014              | Sheep, P. aeruginosa i.t.         | hBM-MSCs        | i.t.        | 5 or 10 × 10⁶ cells/kg, 1 h after injury | ↑ oxygenation ↓ pulmonary edema ↓ lung inflammation, IL-1α, IL-1β, IL-6 and TNF-α levels, apoptosis ↑ survival, VEGF level                                                                                          |
| Chang et al. 2014                 | Sprague-Dawley rat, hypoxenia     | hUC-MSCs        | i.t.        | $5 \times 10^5$ cells, at day 5 postnatal | ↑ survival, VEGF level                                                                                                                     |
| Chao et al. 2014                   | Wistar rat, CLP                   | hBM-MSCs or hUC-MSCs | i.v.        | $5 \times 10^6$ cells, 4 h after injury | ↑ survival, Treg cells expansion ↓ TNF-α and IL-6 levels                                                                                                                                                      |
| Pedrazza et al. 2014              | C57BL/6 mouse, E. coli i.p.       | AD-MSCs         | Retro-orbital | $1 \times 10^6$ cells       | ↓ MCP-1, IL-6 and TGF-β1 levels, splenocytes apoptosis ↑ IL-10 level                                                                                                                                                        |
| Sepúlveda et al. 2014             | BALB/c mouse, LPS i.p.            | Nonsenescent and senescent hBM-MSCs | i.p.        | $1 \times 10^5$ cells, 0.5 h after injury | ↑ survival ↓ TNF-α and IL-6 levels Senescent MSCs had an impaired migration capacity in response to pro-inflammatory signals                                                                                     |
| Alcayaga-Miranda et al. 2015      | C57BL/6 mouse, CLP                | hMens-MSCs with or without antibiotics | i.t. or i.p. | $7.5 \times 10^5$ cells, 3 h after injury | ↑ survival, bacterial clearance, live function ↓ TNF-α, MCP-1, IL-6 and IL-10 levels                                                                                                                                   |
| Devaney et al. 2015               | Sprague-Dawley rat, E. coli i.t.  | hBM-MSCs        | i.v.        | $1 \times 10^7$ or $2 \times 10^7$ cells, 0.5 h after injury | ↑ lung recovery, IL-10, KGF and LL-37 levels ↑ bacterial clearance (only in $2 \times 10^7$ cells)                                                                                                                  |
|                                  |                                   |                 | i.v.        | $2 \times 10^6$, $5 \times 10^6$ or $1 \times 10^7$ cells, 0.5 h after injury | ↑ survival, bacterial clearance and lung recovery ↑ IL-10 and KGF levels (only in $1 \times 10^7$ cells) ↓ IL-6 levels                                                                                     |
| Reference       | Injury model                  | Treatment                  | Route                  | Regimen                          | Main findings                                                                 |
|-----------------|-------------------------------|----------------------------|------------------------|----------------------------------|-------------------------------------------------------------------------------|
| Fang et al. 2015| C57BL/6 mouse, LPS i.t.       | hBM-MSCs                   | i.v. or i.t.           | $1 \times 10^7$ cells, 0.5 h after injury | ↑ survival, bacterial clearance and lung recovery, IL-10 and KGF levels ↓ IL-6 levels |
| Güldner et al. 2015 | BALB/c mouse, CLP          | hBM-MSCs or murine BM-MSCs | i.v.                   | $1 \times 10^5$ cells, 24 h after injury | h: ↓ Est,L, pulmonary edema, TNF-α, VEGF and PDGF levels, ↑ IL-10 level m: ↓ pulmonary edema, TNF-α, IL-6 and VEGF levels |
| Hayes et al. 2015| Sprague-Dawley rat, VILI    | BM-MSCs or CM from MSCs    | i.v.                   | $1 \times 10^7$ cells or 0.5 mL CM, ~3 h after initiation of VILI | MSCs: ↑ lung recovery, ↓ pulmonary edema, lung inflammation, IL-1β and IL-6 levels |
| Monsel et al. 2015 | C57BL/6 mouse, E. coli i.t. | hBM-MSCs or EV-MSCs        | i.t. or i.v.           | $8 \times 10^5$ cells, 4 h after injury | ↑ survival, bacterial clearance, KGF level ↓ lung inflammation, TNF-α and MIP-2 levels |
| Wang et al. 2015 | C57BL/6 mouse, CLP           | Dermal-MSCs                | i.v.                   | $2 \times 10^6$ cells, 4 h after injury | ↑ survival, macrophage migration and phagocytosis capacity, IL-4, IL-5 and IFN-γ levels ↓ IL-1β and IL-6 levels |
| Chan et al. 2016 | BAL/c mouse, influenza A H5N1| hBM-MSCs                   | i.v.                   | $5 \times 10^5$ cells, 4 post infection | ↑ survival, Ang-1 and KGF levels ↓ lung inflammation, pulmonary edema and permeability |
| Cónor et al. 2016 | Wistar rat, CLP             | hWJ-MSCs                   | i.p.                   | $1 \times 10^6$ cells, 6 h after injury | ↑ survival, IL-4, IL-10 and VEGF levels ↓ liver and kidney dysfunction, IL-1α, IL-6, IFN-γ and NF-κB levels |
| Jackson et al. 2016 | C57BL/6 mouse, E. coli i.t. | hBM-MSCs                   | i.v.                   | $1 \times 10^6$ cells, 4 h after injury | MSC transfer their mitochondria to macrophages ↑ macrophage phagocytosis activity ↓ bacteremia |
| Sung et al. 2016 | ICR mouse, E. coli i.t.      | hUC-MSCs                   | i.t.                   | $1 \times 10^5$ cells, 3 h after injury | ↑ TLR4 and β-defensin 2 levels ↓ bacteremia, alveolar wall thickening, mediator levels (IL-1α, IL-1β, IL-6, TNF-α) |
| Yang et al. 2016 | Sprague-Dawley rat, LPS i.t. | BM-MSCs                    | i.v.                   | $5 \times 10^6$ cells, 5 h after injury | ↑ VEGF level ↓ vascular permeability, endothelial cell apoptosis |
| Lee et al. 2017 | Sprague-Dawley rat, 100% O₂ 48h + CLP | hUC-MSCs | i.v. | $1.2 \times 10^6$ cells, 1 or 24 h after injury | ↑ survival (only in group receiving cells 1 h after injury) ↓ kidney injury, TNF-α, IL-6 and IL-1β, MIF, MMP-9, NK-κB and iNOS levels |
| Pedrazza et al. 2017 | C57BL/6 mouse, LPS i.t.    | AD-MSCs                    | Retro-orbital          | $5 \times 10^5$ cells             | ↑ survival ↓ lung inflammation, NETs formation, TNF-α and IL-6 levels, NF-κB and COX-2 expression |
| Xiang et al. 2017 | hMens-MSCs                   | i.v.                       | $1 \times 10^6$ cells, 4 h after injury | | |
| Reference          | Injury model                  | Treatment                          | Route | Regimen                        | Main findings                                                                                                                                                                                                 |
|--------------------|-------------------------------|------------------------------------|-------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zhang et al. 2017  | C57BL/6 mouse, LPS i.t.       | hUC-MSCs with and without FTY720   | i.v.  | $2 \times 10^5$ cells, 24 h or 6 days after injury | ↓ lung inflammation, pulmonary edema, apoptosis, MPO activity and IL-1β level  
↑ IL-10 level  
↑ survival  
↓ lung inflammation, pulmonary edema and permeability, TNF, IL-6, and MCP-1 levels  
Combined therapy with MSCs and FTY720 yielded better therapeutic responses |
| Huang et al. 2018  | C57BL/6 mouse, LPS i.t.       | hUC-MSCs with and without FTY720   | i.v.  | $2 \times 10^5$ cells, 24 h after injury | Alteration of ARDS-related genes at the transcriptional level, mainly Nr1h4, Nol3, Cyp17a1, Prkg2, and Rps6ka6                                                                                               |
| Silva et al. 2018a | Wistar rat, LPS i.t.          | BM-, AD-, and lung-derived MSCs    | i.v.  | $1 \times 10^5$ cells 48 h after injury | ↓ Est,L, alveolar collapse, lung inflammation, TNF-α, IL-1β, KC, and TGF-β levels, collagen and elastic fiber content, apoptosis (lung, kidney, liver)  
↑ KGF level  
BM- and AD-MSCs were more effective than lung-MSCs |
| Mokhber-Dezfouli et al. 2018 | New Zealand rabbit, LPS i.t.  | BM-MSCs                           | i.t.  | $1 \times 10^{10}$ cells, 24 h after injury | ↑ O₂ saturation, IL-10 level  
↓ severity of clinical symptoms, total and differential cell count in blood and BALF, lung inflammation, pulmonary edema, IL-6 and TNF-α levels |
| Islam et al. 2019  | C57BL/6 mouse, HCl instillation, VILI, or both | BM-MSCs                           | i.t.  | $5 \times 10^5$ cells i.t. and $5 \times 10^5$ cells i.v., 48 h after injury | Proteome differs significantly depending on type and stage of lung injury  
↓ fibrosis in VILI model alone  
↑ fibrosis in HCl model, regardless if with or without VILI |
| Wang et al. 2019   | Sprague-Dawley rat, LPS i.t.  | Lung-derived MSCs                 | i.v.  | $5 \times 10^5$ cells 4 h after injury | ↓ lung inflammation, pulmonary edema, IL-1β, IL-6, and TNF-α levels  
↑ KGF-2 and surfactant protein-C levels  
Restored Treg/Th17 balance (↑ Treg and ↓ Th17 cell counts) |

AD, adipose tissue-derived; Ang-1, angiopoietin-1; BALF, bronchoalveolar lavage fluid; BM, bone marrow-derived; CLP, cecal ligation and puncture; CM, conditioned media; ENaC, epithelial sodium channel; Est,L, static lung elastance; EV, extracellular vesicles; h, human; HO, heme oxygenase; IFN, interferon; IL, interleukin; IL-1RN, IL-1 receptor antagonist; i.p., intraperitoneal; i.t., intratracheal; i.v., intravenous; KGF, keratinocyte growth factor; LPS, lipopolysaccharide; LXA₄, lipoxin A₄; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; Mens, menstrual blood-derived; MIP, macrophage inflammatory protein; MMP, metalloproteinase; MPO, myeloperoxidase; MSCs, mesenchymal stem cells; NET, neutrophil extracellular trap; NF-κB, nuclear factor-κB; o.a., oropharyngeal aspiration; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; TSG-6, TNF-inducible gene 6; UC, umbilical cord-derived; VEGF, vascular endothelial growth factor; VILI, ventilator-induced lung injury
proliferation (Chen et al. 2014), while inducing regulatory T cell expansion (Sun et al. 2011; Chao et al. 2014; Wang et al. 2019) and reprogramming other macrophages into the M2 phenotype (Németh et al. 2009; Vasandian et al. 2016). Although several studies have indicated an increase in IL-10 levels after MSC therapy, others have demonstrated a reduction in the inflammatory process with no change (Gupta et al. 2012; Krasnodembskaya et al. 2012) or even a decrease in IL-10 levels (Mei et al. 2010; Sepúlveda et al. 2014). Similarly, variable effects have been observed regarding IFN-γ levels, with studies reporting reduction (Gonzalez-Rey et al. 2009; Sun et al. 2011; Cóndor et al. 2016), no change (Németh et al. 2009; Pedrazza et al. 2014), or even an increase (Wang et al. 2015). In fact, there are several differences among these experimental studies that can explain such heterogeneity: (1) disease severity, etiology, and initial insult; (2) MSC dose, source, and route of administration; (3) timing of therapy (prophylactic or therapeutic) and analysis methods. Although the underlying mechanisms and degree of therapeutic benefit obtained may differ, in most cases, MSCs were nevertheless able to efficiently induce anti-inflammatory effects.

Anti-apoptotic effects

Apoptosis of both resident and immune cells plays a critical role in ARDS progression, as it leads to recruitment of inflammatory cells and tissue remodeling. Although the mechanisms by which MSC therapy exert anti-apoptotic effects need to be further investigated, MSCs have demonstrated ability to reduce apoptotic cell counts in the lung and distal organs (Pedrazza et al. 2014; Xiang et al. 2017; Silva et al. 2018a; Zhang et al. 2018). MSCs have also been shown to protect alveolar macrophages from endotoxin-induced apoptosis partially by inhibiting the Wnt/β-catenin pathway (Li et al. 2015). Increased secretion of keratinocyte growth factor (KGF) after MSC therapy was demonstrated to decrease monocyte apoptosis by protein kinase B phosphorylation (Lee et al. 2013). Furthermore, either MSCs or their conditioned media can protect resting and activated neutrophils in vitro from undergoing apoptosis by cell contact-independent mechanisms (Raffaghello et al. 2008). Several studies have also demonstrated that MSC therapy mitigates TNF-α levels (Kim et al. 2011; Zhao et al. 2013; Gülßner et al. 2015), which might contribute to its anti-apoptotic effects, as TNF-α can induce cell death by activating the Fas/FasL pathway.

Antimicrobial effects

Infection is the most common cause of ARDS, and although MSCs themselves lack phagocytic activity, they can stimulate phagocytosis by host immune cells and production of antimicrobial peptides.

MSC therapy has been demonstrated to significantly reduce bacterial load in animal models of infection induced by Escherichia coli (Cai et al. 2015; Devaney et al. 2015), Pseudomonas aeruginosa (Krasnodembskaya et al. 2012; Asmussen et al. 2014), Staphylococcus aureus (Qian et al. 2016), and polymicrobial sepsis (Gonzalez-Rey et al. 2009; Németh et al. 2009; Alcayaga-Miranda et al. 2015), as well as in an ex vivo perfused human lung model (Lee et al. 2013). Such effects appeared to be mediated by secretion of antimicrobial peptides, including LL-37 (Krasnodembskaya et al. 2010) and lipocalin-2 (Gupta et al. 2012), since antimicrobial actions were abrogated when neutralizing antibodies were used. Secretion of β-defensin-2 via TLR4 signaling has also been implicated in MSC-induced bacterial clearance (Sung et al. 2016). Furthermore, MSCs have been shown to reduce bacterial load in vivo by enhancing the phagocytic activity of macrophages (Mei et al. 2010; Lee et al. 2013) and monocytes (Krasnodembskaya et al. 2012). In both in vivo and in vitro models, MSCs also enhanced phagocytic activity of macrophages and monocytes by promoting mitochondrial transfer via tunneling nanotubes, thus resulting in a more effective bacterial clearance (Jackson et al. 2016).

Restoration of epithelial and endothelial cell permeability

Disruption of alveolar-capillary membrane integrity is a hallmark of ARDS and contributes to edema formation and tissue remodeling. MSC therapy has been shown to preserve or restore the alveolar epithelial and vascular endothelial lining, thus reducing lung dysfunction in ARDS models.

In vitro studies have demonstrated that co-culture of endothelial cells with MSCs induced protective actions against inflammatory disruption of barrier function by modulating vascular endothelial cadherin/β-catenin signaling (Pati et al. 2011a). MSC therapy also reduced lung endothelial cell permeability in ex vivo perfused
human lungs injured by either endotoxin or live *E. coli*, while inhibiting neutrophil influx and enhancing production of fibroblast growth factor (FGF)-7 (Lee et al. 2009a, 2013). Furthermore, in vivo studies demonstrated that MSCs were able to mobilize adherens and tight junction proteins and reduce the binding of inflammatory cells to the endothelium, resulting in preservation of vascular endothelial integrity (Pati et al. 2011b). Controversies persist regarding the impact of MSC therapy on vascular endothelial growth factor (VEGF) levels. Some studies have reported a reduction in VEGF levels after MSC administration when comparing treated vs. untreated injured groups (Lee et al. 2010; Silva et al. 2018a), while other authors have observed an increase (Chang et al. 2014; Yang et al. 2016; Wang et al. 2018a). Further research is needed to better understand the role of VEGF after MSC administration, as it has been correlated with increased vascular endothelial permeability (Lee et al. 2010), angiogenesis and wound healing (Chang et al. 2014; Wang et al. 2018a), and protection of lung vascular endothelium against apoptosis (Yang et al. 2016).

MSCs have been shown to restore epithelial cell protein permeability in human type II pneumocytes exposed to a mix of pro-inflammatory factors (IL-1β, IFN-γ, and TNF-α) by contact-independent mechanisms and mediated by the secretion of angiopoietin-1 (Ang-1) (Fang et al. 2010). In another study, MSC-conditioned media was able to restore sodium transport and preserve epithelial permeability of rat alveolar epithelial cells exposed to a mix of pro-inflammatory factors and hypoxia by increasing levels of IL-1RN and PGE2 (Goolaerts et al. 2014). Furthermore, MSC therapy has been shown to reduce fibrosis, while increasing macrophage polarization to the M2 phenotype, which is involved in wound repair and inflammation resolution (Maron-Gutierrez et al. 2013). In this study, MSCs also increased expression of metalloproteinase (MMP)-8 and decreased expression of tissue inhibitor of metalloproteinase (TIMP)-1 (Maron-Gutierrez et al. 2013). Other studies have demonstrated a reduction in lung tissue remodeling (collagen and elastic fiber content) accompanied by decreasing IL-1β and transforming growth factor (TGF)-β levels after MSC administration (Silva et al. 2018a).

In an endotoxin-induced lung injury model, MSCs abrogated alveolar leukocytosis and protein leak by contact-dependent mechanisms (Islam et al. 2012). MSCs formed connexin 43-containing gap junctional channels with alveolar cells in vivo, releasing mitochondria-containing microvesicles that restored ATP concentrations, surfactant secretion, and alveolar bioenergetics (Islam et al. 2012). Increased expression of surfactant protein-C was also observed when injured lung tissue was co-cultured with MSCs and after MSC therapy in hyperoxia-induced lung injury (Zhang et al. 2012).

Increased alveolar fluid clearance and lung recovery

Removal of excessive alveolar and interstitial fluid is crucial for lung recovery and function, since fluid significantly affects surfactant concentration and prevents appropriate gas exchange. Several studies have indicated that MSCs improve alveolar fluid clearance by modulating expression of paracrine factors and function of membrane channels and transporters.

Administration of MSCs or MSC-conditioned media was able to reduce lung water and normalize alveolar fluid clearance in ex vivo perfused human lungs injured by endotoxin or live *E. coli* (Lee et al. 2009a, 2013). MSCs also normalized alveolar fluid clearance in perfused lungs rejected for transplant, an effect that was significantly reduced when the perfused lung was pretreated with FGF7-neutralizing antibody (McAuley et al. 2014).

In vitro, either co-culture with MSCs or exposure to MSC-conditioned media preserved fluid transport by preventing the reduction in apical expression of αENaC subunits. Notably, depletion of FGF7 expression abrogated these therapeutic benefits (Lee et al. 2009a; Goolaerts et al. 2014). Furthermore, in a model of influenza infection-induced lung injury, MSCs prevented impairment of alveolar fluid clearance and protein permeability by enhancing secretion of Ang-1 and KGF and by preventing downregulation of Na+/K+-ATPase (Chan et al. 2016).

In a model of ventilation-induced lung injury, intratracheally administered MSCs and MSC-conditioned media similarly enhanced alveolar fluid clearance, reduced alveolar thickening and inflammation, and restored lung function partly by KGF-dependent mechanism (Curley et al. 2013). Nevertheless, compared to MSCs, MSC-conditioned media (administered intravenously) was unable to improve lung edema and inflammation, arterial oxygenation, or static compliance in a subsequent study conducted by the same group (Hayes et al. 2015). Similar findings were
observed in models of endotoxin-induced lung injury (Silva et al. 2019a).

Improvement of lung and distal organ injury and survival

As ARDS progresses, multiple organ dysfunction can occur, ultimately resulting in increased morbidity and mortality. MSC administration has been demonstrated to protect or even reduce morphological and functional abnormalities in the lung (Maron-Gutierrez et al. 2013; Silva et al. 2018a), kidney (Luo et al. 2014; Cóndor et al. 2016; Silva et al. 2018a), liver (Alcayaga-Miranda et al. 2015; Cóndor et al. 2016; Silva et al. 2018a), heart (Lee et al. 2009b; Weil et al. 2011), spleen (Mei et al. 2010; Pedrazza et al. 2014), and bowel (Gonzalez-Rey et al. 2009; Anderson et al. 2013). These therapeutic effects have a significant impact on the reduction of mortality rate, as observed in many experimental studies (Németh et al. 2009; Mei et al. 2010; Gupta et al. 2012; Chao et al. 2014; Alcayaga-Miranda et al. 2015; Chan et al. 2016; Pedrazza et al. 2017).

Clinical trials of MSC therapy in patients with ARDS

To date, 13 clinical trials assessing the safety and efficacy of MSC therapy in ARDS patients are registered in the US National Institutes of Health ClinicalTrials.gov platform (https://clinicaltrials.gov) (Table 3). Although all are early-phase clinical studies and are limited by small sample sizes, their major goal is primarily to assess the safety of MSC administration and, secondarily, to assess their efficacy on clinical outcomes, such as respiratory and systemic parameters, inflammation, and hemodynamics. Like most experimental studies, however, these clinical investigations present substantial heterogeneity concerning inclusion and exclusion criteria, length of follow-up, and MSC dose, source, route of administration, and frequency.

The earliest study to assess the safety of MSCs in patients with ARDS was conducted in China (NCT01902082) (Zheng et al. 2014). In this phase I, single-center, randomized, double-blind, placebo-controlled trial, patients received a systemic infusion of allogenic adipose tissue-derived MSCs (1 × 10^6 cells kg^-1). Although MSC administration appeared to be safe and well tolerated, impact on clinical outcomes was weak, with no significant differences between the two groups in length of hospital stay, ventilator-free days, or intensive care unit-free days, nor on serum concentration of relevant biomarkers (IL-6, IL-8, and surfactant protein-D) (Zheng et al. 2014). The absence of any evaluation of time- and dose-response relationships for MSC therapy as well as the short follow-up period (28 days) are major limitations of this clinical study.

Another study assessing the safety of MSCs in ARDS patients was conducted in the USA (NCT01775774) (Wilson et al. 2015). In this phase I, multicenter, open-label, dose-escalation clinical study, patients with moderate to severe ARDS received a single intravenous infusion of allogeneic bone marrow-derived MSCs (1, 5, or, 10 × 10^6 cells kg^-1). Although no significant differences were observed in concentrations of measured biomarkers (IL-6, IL-8, ANGPT2, and AGER), all MSC dose levels were well tolerated, with no infusion-related adverse events. The same research group conducted a subsequent clinical trial with the highest MSC dose (10 × 10^6 cells kg^-1), as it was associated with a more favorable trend in lung injury score and sequential organ failure assessment score compared to lower doses (Wilson et al. 2015). In this subsequent phase IIa, multicenter, randomized, double-blind, placebo-controlled trial (NCT02097641) (Matthay et al. 2019), patients with moderate to severe ARDS received a single intravenous infusion of allogeneic bone marrow-derived MSCs (10 × 10^6 cells kg^-1). No patient experienced any of the predefined MSC-related hemodynamic and respiratory adverse events. A trend for improvement in oxygenation index, albeit not significant, was observed in the patients that received MSCs. Furthermore, concentrations of angiopoietin-2 in plasma were significantly reduced in MSC recipients, indicating a reduction in endothelial injury (Matthay et al. 2019).

MSCs have also been tested in compassionate-use settings. In a Swedish case report, two patients with severe, refractory ARDS who failed to improve after standard life support measures received systemic administration of allogeneic bone marrow-derived MSCs (2 × 10^6 cells kg^-1) obtained from a healthy volunteer (Simonson et al. 2015). Both patients recovered from hemodynamic, respiratory, and multiple organ failure. These outcomes were associated with a reduction in several pulmonary and systemic biomarkers of inflammation (Simonson et al. 2015).
Barriers and future directions for MSC therapy in ARDS

MSC therapy holds promise for the treatment of ARDS for many reasons, as described above. Despite important advances, further research is needed to elucidate several unanswered questions, including the optimal MSC source and dose, route of administration, and frequency (single vs. multiple-dose regimen). Moreover, in many experimental protocols, MSCs were administered before, at the time of, or only a few hours after disease induction; these models fail to take into account the time course of lung and distal organ injury and, therefore, do not resemble the clinical situation.

Although bone marrow has been the most common source used to obtain MSCs (McIntyre et al. 2016), an invasive harvesting procedure is required, and these cells have limited availability. Furthermore, experimental ARDS has been shown to modify the profile of the bone marrow cell population, affecting their immunomodulatory effects and limiting their potential use for autologous transplantation (Silva et al. 2014; Antebi et al. 2018). MSCs from different sources have been intensively investigated, as these cells exhibit differences in gene expression and stability, secretome, and cell surface proteins, which may impact on their survival and regenerative properties (Ostanin et al. 2011; Nora et al. 2012; Elahi et al. 2016; Heo et al. 2016). However, few studies have comparatively evaluated the effects of MSCs from different sources (Nystedt et al. 2013; Chao et al. 2014; Silva et al. 2018a), and whether cells from any one source may provide superior therapeutic responses remains unclear. In addition, cell dosing has meaningful clinical relevance and remains under-investigated, as clinical trials conducted to date have focused on safety, with efficacy as a secondary assessment.

MSCs have been administered as a single dose ranging from $5 \times 10^4$ to $3.6 \times 10^7$ cells in experimental models (McIntyre et al. 2016). From a translational perspective, this range in a 25-g mouse would correspond to $2 \times 10^6$ to $1.44 \times 10^9$ cells kg$^{-1}$ (or 150 million to 108 billion cells for a 75-kg human). Such quantities are technically and operationally challenging, and administration of high doses of MSCs is associated with several safety

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**Table 3** Clinical trials evaluating the safety and efficacy of mesenchymal stem cell-based therapies in patients with acute respiratory distress syndrome

| ClinicalTrials.gov ID | Country | Phase | Treatment | Dose, frequency, and route | Patients enrolled | Follow-up |
|-----------------------|---------|-------|-----------|---------------------------|------------------|-----------|
| Completed             |         |       |           |                           |                  |           |
| NCT01775774 (Wilson et al. 2015) | USA | I     | BM-MSCs   | 1, 5, or 10 × 10^6 cells kg$^{-1}$, i.v., single dose | 9 (3/3/3) | 12 months |
| NCT01902082 (Zheng et al. 2014)  | China | I     | AD-MSCs   | 1 × 10^6 cells kg$^{-1}$, i.v., single dose | 12 (6/6) | 28 days |
| NCT02097641 (Matthay et al. 2019) | USA | IIa   | BM-MSCs   | 10 × 10^6 cells kg$^{-1}$, i.v., single dose | 60 (40/20) | 12 months |
| Ongoing               |         |       |           |                           |                  |           |
| NCT02095444 China I/II | Mens-MSCs | 10 × 10^6 cells kg$^{-1}$, i.v., twice a week for 2 weeks | 20 | 14 days |
| NCT02112500 Korea II | BM-MSCs | i.v. | 10 | 28 days |
| NCT02215811 Sweden I | BM-MSCs | Not reported | 10 | 12 months |
| NCT02444455 China II | UC-MSCs | 5 × 10^6 cells kg$^{-1}$, i.v., once daily for 3 days | 20 | 14 days |
| NCT02611609 UK/USA I/II | MultiStem | Not reported | 36 | 12 months |
| NCT02804945 USA II | BM-MSCs | 3 × 10^6 cells kg$^{-1}$, i.v., single dose | 20 | 60 days |
| NCT03042143 UK II | UC-MSCs | 1.5, or 10 × 10^6 cells kg$^{-1}$, i.v., single dose | 75 | 28 days |
| NCT03552848 China | UC-MSCs | 1 × 10^6 cells, i.v., once every 4 days for four times | 15 | 24 months |
| NCT03608592 China I | UC-MSCs | 60 × 10^6 cells, i.v., single dose | 12 | 28 days |
| NCT03818854 USA IIb | BM-MSCs | 10 × 10^6 cells kg$^{-1}$, i.v., single dose | 120 (60/60) | 60 days |

MSCs, mesenchymal stromal cells; AD, adipose tissue-derived; BM, bone marrow-derived; Mens, menstrual blood-derived; UC, umbilical cord-derived; i.v., intravenous
concerns. To date, $1 \times 10^7$ cells kg$^{-1}$ is the highest dose ever used in clinical studies. As in pharmacological research, determination of the therapeutic window and index for MSC therapies is a critical step that should be further characterized in experimental studies to ensure that the greatest therapeutic benefits can be achieved without resulting in side effects in the clinical setting.

MSC administration has been performed by either local or systemic routes in different experimental models. While local administration (e.g., intratracheal) delivers cells directly to the site of injury, systemic administration (e.g., intravenous) allows wide distribution throughout the body. However, MSCs administered intravenously are subjected to the pulmonary first-pass effect (Fischer et al. 2009), which results in significant retention of cells. In fact, this effect may offer an advantage for lung tissue repair. Although ongoing clinical trials and most number of experimental studies have used the intravenous route (McIntyre et al. 2016), therapeutic responses were similar in the few studies that compared different routes for MSC delivery in animal models (Curley et al. 2013; Alcayaga-Miranda et al. 2015; Devaney et al. 2015). Importantly, ECMO has become an increasingly common therapeutic modality for patients with severe ARDS (Bellani et al. 2016; Papazian et al. 2019). In an ex vivo model, MSCs administered intravascularly were found to adhere to membrane oxygenator fibers during ECMO, resulting in a significant reduction of flow through the circuit (Millar et al. 2019). Further investigations should be performed with alternative routes of administration, such as intrabronchial, to identify which would be a viable option for this clinical situation. Finally, most experimental studies have focused on short-term effects of MSC therapy; evaluation of long-term effects has been comparatively neglected. Although a single dose of MSCs has been shown to result in therapeutic responses, more than one dose may be required to induce a more efficient tissue repair or even to maintain benefits, as observed in animal models of elastase-induced emphysema and silicosis (Lopes-Pacheco et al. 2013; Poggio et al. 2018).

As the surrounding environment can have a significant impact on MSC phenotype and behavior (Mathieu and Loboa 2012; Galleu et al. 2017; Leuning et al. 2018; de Castro et al. 2019; Islam et al. 2019), recent experimental studies have employed different methods to enhance the therapeutic actions of MSCs (Silva et al. 2018b) (Table 4). Under hypoxic conditions, MSCs have been shown to upregulate expression of genes related to pro-survival, anti-apoptotic, antioxidant signaling, resulting in reduction of fibrosis and expression of pro-inflammatory mediators in a model of bleomycin-induced lung injury (Lan et al. 2015). In experimental sepsis, MSC preconditioning with poly (I:C), a TLR3 ligand, inhibited expression of miR-143 and increased expression of cyclooxygenase-2, resulting in increased PGE2 production and macrophage anti-inflammatory actions (Zhao et al. 2014). Compared to naïve MSCs, eicosapentaenoic acid-preconditioned MSCs induced further reduction in lung inflammation and remodeling as well as in lung and distal organ injury, thus resulting in greater improvement in severity score and survival in CLP-induced experimental sepsis (Silva et al. 2019b). Other studies have also demonstrated enhancement of therapeutic effects by inducing overexpression of certain genes by MSCs, including Ang-1 (Mei et al. 2007), IL-33 antagonist soluble IL-1R1 (Martinez-González et al. 2013), IL-10 (Wang et al. 2018b; Jerkic et al. 2019), Nrf2 (Zhang et al. 2018), and HGF (Meng et al. 2019). As the degree of therapeutic outcomes can differ depending on disease severity, etiology, and primary insult, different preconditioning approaches may provide a more appropriate MSC therapy according to the disease features of each patient, thus driving more effective therapeutic and regenerative responses.

Despite tremendous progress in investigating cell-based therapy in ARDS, the safety of MSC therapy has been only demonstrated in early-stage clinical studies with a relatively small number of patients. Therefore, the safety and efficacy of MSC therapy has yet to be demonstrated in large-scale clinical trials. Furthermore, if they ever prove to be an efficient therapy, MSCs must still be available within few hours, in enough quantity, and obtained in an affordable manner from a well-regulated and controlled production process if they are to become a viable therapy for patients with acute or critical illnesses, including ARDS (Ginty et al. 2011). Several barriers in the process of standardization, scalability, manufacturing, distribution, cost, and regulation, which still preclude the efficient, routine use of MSC therapy, have been discussed elsewhere (Heathman et al. 2015; Isasi et al. 2016).

**Conclusion**

MSC-based therapies constitute promising strategies for the treatment of ARDS, given their demonstrated
| Reference | Injury model | Treatment | Enhancement method | Route | Regimen | Main findings |
|-----------|--------------|-----------|--------------------|-------|---------|---------------|
| Mei et al., 2007 | C57BL/6 mouse, LPS i.t. | BM-MSCs | Overexpression of Ang-1 | i.v. | $2.5 \times 10^5$ cells, 30 min after injury | Further reduction in LPS-induced pulmonary permeability |
| Martinez-González et al., 2013 | BALB/c mouse, LPS i.n. | hAD-MSCs | Overexpression of IL-33/IL-1 receptor-like-1 | i.v. | $1 \times 10^6$ cells, 6 h after injury | Further reduction in lung inflammation, apoptosis, vascular leakage, TNF-α, IL-6 and MIP-2 levels |
| Zhao et al., 2014 | C57BL/6 mouse, CLP | hUC-MSCs | Preconditioning with poly (I:C) | i.v. | $1 \times 10^6$ cells, 1 h after injury | Preserved alveolar architecture |
| Lan et al., 2015 | C57BL/6 mouse, bleomycin | BM-MSCs | Preconditioning with poly (I:C) | i.t. | $5 \times 10^5$ cells, 3 days after injury | Further reduction in bacteria load and increased survival |
| Wang et al., 2018b | C57BL/6 mouse, LPS i.t. | BM-MSCs | Overexpression of IL-10 | i.t. | $1 \times 10^6$ cells, 4 h after injury | Further reduction in bacteria load and increased survival |
| Zhao et al., 2014 | C57BL/6 mouse, LPS i.t. | BM-MSCs | Overexpression of Ang-1 | i.v. | $2.5 \times 10^5$ cells, 30 min after injury | Further reduction in LPS-induced pulmonary permeability |
| Martinez-González et al., 2013 | BALB/c mouse, LPS i.n. | hAD-MSCs | Overexpression of IL-33/IL-1 receptor-like-1 | i.v. | $1 \times 10^6$ cells, 6 h after injury | Further reduction in lung inflammation, apoptosis, vascular leakage, TNF-α, IL-6 and MIP-2 levels |
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| Wang et al., 2018b | C57BL/6 mouse, LPS i.t. | BM-MSCs | Overexpression of IL-10 | i.t. | $1 \times 10^6$ cells, 4 h after injury | Further reduction in bacteria load and increased survival |
| Zhao et al., 2014 | C57BL/6 mouse, LPS i.t. | BM-MSCs | Overexpression of Ang-1 | i.v. | $2.5 \times 10^5$ cells, 30 min after injury | Further reduction in LPS-induced pulmonary permeability |
| Martinez-González et al., 2013 | BALB/c mouse, LPS i.n. | hAD-MSCs | Overexpression of IL-33/IL-1 receptor-like-1 | i.v. | $1 \times 10^6$ cells, 6 h after injury | Further reduction in lung inflammation, apoptosis, vascular leakage, TNF-α, IL-6 and MIP-2 levels |
| Zhao et al., 2014 | C57BL/6 mouse, CLP | hUC-MSCs | Preconditioning with poly (I:C) | i.v. | $1 \times 10^6$ cells, 1 h after injury | Preserved alveolar architecture |
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| Wang et al., 2018b | C57BL/6 mouse, LPS i.t. | BM-MSCs | Overexpression of IL-10 | i.t. | $1 \times 10^6$ cells, 4 h after injury | Further reduction in bacteria load and increased survival |
| Zhao et al., 2014 | C57BL/6 mouse, LPS i.t. | BM-MSCs | Overexpression of Ang-1 | i.v. | $2.5 \times 10^5$ cells, 30 min after injury | Further reduction in LPS-induced pulmonary permeability |
| Martinez-González et al., 2013 | BALB/c mouse, LPS i.n. | hAD-MSCs | Overexpression of IL-33/IL-1 receptor-like-1 | i.v. | $1 \times 10^6$ cells, 6 h after injury | Further reduction in lung inflammation, apoptosis, vascular leakage, TNF-α, IL-6 and MIP-2 levels |
| Zhao et al., 2014 | C57BL/6 mouse, CLP | hUC-MSCs | Preconditioning with poly (I:C) | i.v. | $1 \times 10^6$ cells, 1 h after injury | Preserved alveolar architecture |
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| Lan et al., 2015 | C57BL/6 mouse, bleomycin | BM-MSCs | Preconditioning with poly (I:C) | i.t. | $5 \times 10^5$ cells, 3 days after injury | Further reduction in bacteria load and increased survival |
| Wang et al., 2018b | C57BL/6 mouse, LPS i.t. | BM-MSCs | Overexpression of IL-10 | i.t. | $1 \times 10^6$ cells, 4 h after injury | Further reduction in bacteria load and increased survival |

AD, adipose tissue-derived; Ang-1, angiopoietin-1; BM, bone marrow-derived; CLP, cecal ligation and puncture; COX-2, cyclooxygenase-2; EVs, extracellular vesicles; h, human; HGF, hepatocyte growth factor; HO, heme oxygenase; IL, interleukin; i.n., intranasal; i.p., intraperitoneal; i.t., intratracheal; i.v., intravenous; KGF, keratinocyte growth factor; L, Lats1, large tumor suppressor kinase 1; LPS, lipopolysaccharide; MIP, macrophage inflammatory protein; MSCs, mesenchymal stem cells; Nrf2, nuclear factor erythroid 2-related factor 2; TAK-1, transforming growth factor-β activated kinase-1; TNF, tumor necrosis factor; UC, umbilical cord-derived
therapeutic benefits: anti-inflammatory and anti-apoptotic effects, enhanced epithelial and endothelial cell recovery, microbial and alveolar fluid clearance, and improvements in lung and distal organ injury and survival. The benefits of MSC-based therapies appeared to be induced by complex, well-orchestrated signaling pathways rather than by any one (or few) mechanisms. Key mechanisms of action include secretion of paracrine and endocrine factors as well as transfer of cellular contents via extracellular vesicles or cell-to-cell contact. Despite the progress reviewed herein, many questions have yet to be answered before the therapeutic impact of MSCs can be maximized. The possibility of enhancing the benefits of MSCs by preconditioning methods has brought novel opportunities that should be further explored. Safety results from phase I and II clinical trials are encouraging, but the safety and efficacy profile has yet to be proven in large-scale trials. In an ideal clinical scenario, MSCs would be promptly available and obtained through well-standardized procedures, but some barriers still pose challenges to the feasibility of MSC therapy.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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