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REVIEW

Therapeutic Benefits of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome: Potential Mechanisms and Challenges

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Abstract: Acute respiratory distress syndrome (ARDS) presents as a form of acute respiratory failure resulting from non-cardiogenic pulmonary edema due to excessive alveolocapillary permeability, which may be pulmonary or systemic in origin. In the last 3 years, the coronavirus disease 2019 pandemic has resulted in an increase in ARDS cases and highlighted the challenges associated with this syndrome, as well as the unacceptably high mortality rates and lack of effective treatments. Currently, clinical treatment remains primarily supportive, including mechanical ventilation and drug-based therapy. Mesenchymal stem cell (MSC) therapies are emerging as a promising intervention in patients with ARDS and have promising therapeutic effects and safety. The therapeutic mechanisms include modifying the immune response and assisting with tissue repair. This review provides an overview of the general properties of MSCs and outlines their role in mitigating lung injury and promoting tissue repair in ARDS. Finally, we summarize the current challenges in the study of translational MSC research and identify avenues by which the discipline may progress in the coming years.
Keywords: acute respiratory distress syndrome, mesenchymal stromal cells, therapeutic effect, potential mechanisms

Introduction

Acute respiratory distress syndrome (ARDS) remains a very common cause of respiratory failure and requires intensive medical care. It is a common disease observed clinically and is characterized by acute and refractory hypoxia noncardiogenic pulmonary edema, diffuse alveolar-capillary membrane damage, and reduced compliance.[1] The most common clinicopathological manifestations associated with ARDS development include pneumonia and sepsis.[1] The diagnostic criteria for ARDS have changed since its first description in 1967,[2] and its current definition is characterized by the acute onset of impaired oxygenation (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2/FiO_2] <300 mmHg) and bilateral infiltrates on chest imaging in the absence of left atrial hypertension as the dominant cause of pulmonary edema.[3] Based on the Berlin definition proposed in 2012, ARDS is classified into three categories of severity according to the level of hypoxemia: mild (PaO_2/FiO_2, 201–300 mmHg), moderate (PaO_2/FiO_2, 100–≤200 mmHg), and severe (PaO_2/FiO_2, <100 mmHg).[3] The main clinical manifestations include low oxygenation, low lung compliance, and hyperphysiological dead space caused by damage to the alveolar epithelium and vascular endothelial cells, as well as increased pulmonary vascular permeability.[4]

ARDS remains a relatively frequent and lethal or disabling syndrome in clinical practice. An observational study of patients in 496 intensive care units (ICUs) from 50 different countries reported that clinical recognition rates ranged from 10% of ICU patients to 23% of mechanically ventilated patients according to the criteria for ARDS.[5] However, mortality rates remain sobering: >30% in-hospital,[5] with moderate to severe ARDS reaching a rate of 43% in-hospital mortality at 90 days.[6] Even if they recover, survivors remain burdened by functional limitations resulting from muscle weakness or

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cognitive impairment.[7] Despite five decades of advances in basic and clinical research having passed, there is still no effective goal-directed pharmacotherapy, and therapies remain primarily supportive, including lung protective ventilation and conservative fluid management strategies.[8–10] ARDS is particularly relevant as a consequence of the global coronavirus disease 2019 (COVID-19), affecting hundreds of millions of people worldwide in the last 3 years.

There have been abundant developments in the understanding of the pathogenesis of ARDS over the past 50 years, yielding valuable insights into the mechanisms responsible for the pathogenesis and pathophysiology of this disease. The most prominent pathophysiological feature of ARDS is diffuse alveolar-capillary barrier damage, leading to abundant protein-rich fluid accumulation.[11,12] Once the lung is damaged by infection, trauma, or inflammatory pathogens, inflammatory pathways may be activated, characterizing the exudative phase of ARDS. This phase involves innate immune cell-mediated damage to the alveolar endothelial and epithelial barrier.[13] In particular, although the inflammatory responses aid pathogen clearance, excessive inflammation may also lead to alveolar damage – specifically greater endothelial and epithelial permeability – contributing to the accumulation of protein-rich alveolar edema fluid.[14] As a result of the accumulation of lung edema fluid, dyspnea and gas interchange disturbance result in hypoxemia, reduced carbon dioxide excretion, and ultimately acute respiratory failure (Figure 1).[15,16] Taken together, the data suggest that the

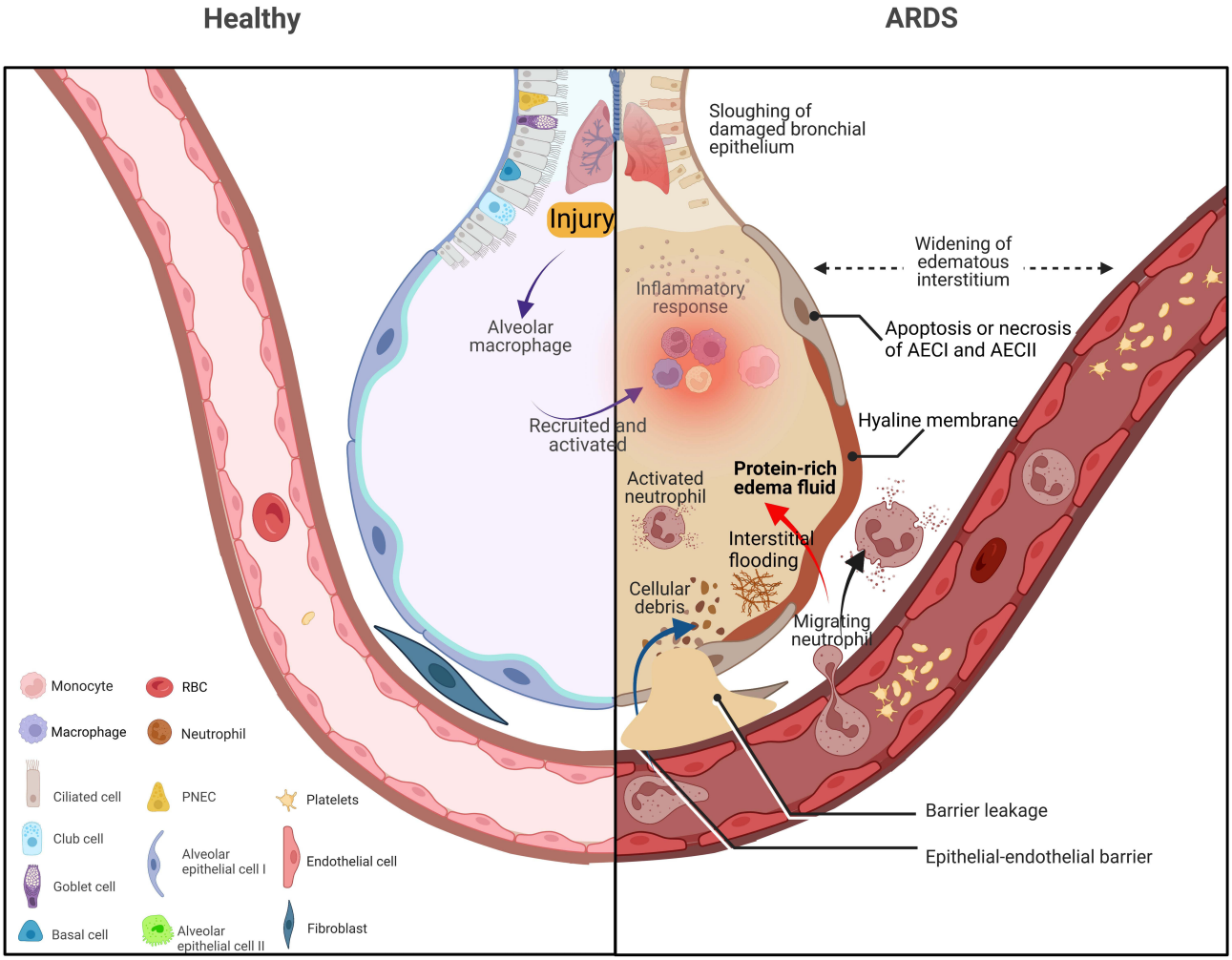

Figure 1 The pathological physiology of acute respiratory distress syndrome. The inflammation-induced damage results in destruction of the alveolar-capillary walls, aggregation of proinflammatory cells, formation of hyaline membranes, and an abundance of protein-rich edema in the interstitium and alveoli. The unregulated and excessive immune reaction that contributes to alveolar injury, then, directly increases the permeability of the alveolar-capillary barrier, and the apoptosis of alveolar epithelial cells type II (AEC II) weakens the secretion of pulmonary surfactant and the clearance of alveolar fluid and exacerbates alveolar stroma and protein-rich edema within the alveoli. (Created using BioRender.com).

Abbreviation: ARDS, acute respiratory distress syndrome.

inflammation-induced endothelial cell damage in the lungs contributes to an increase in vascular permeability, which in turn leads to the formation of pulmonary edema. Effectively, this over-immune response, which is not regulated, leads to alveolar injury, causing severe and life-threatening clinical complications of ARDS.[17]

A growing body of evidence has shown that cell-based therapy is promising for a variety of inflammatory conditions, including ARDS. Interestingly, mesenchymal stem cell (MSC) treatment is under consideration as a promising intervention for treating ARDS based on our further understanding of the pathogenesis of this condition.[18,19]

Multiple studies have also confirmed that MSCs may reduce inflammation, apoptosis, and microorganism infection and promote angiogenesis, promote the clearance of bacteria and alveolar fluid, repair the lung endothelial and epithelial cells, and prevent lung and distal organ injury in patients with ARDS.[20–22] Importantly, some early-phase clinical trials have also been completed or are in progress to assess the safety and efficacy of MSC treatment in patients with ARDS.[23,24] However, certain issues remain to be elucidated; for example, we should examine which is the best administration route for the MSCs, if there are any adverse reactions after administration, which is the focus of the potential therapeutic effects, and indicate the populations or preparations of MSCs that present the best efficacy in any given clinical situation.[25,26]

In this review, we discuss the mechanisms of MSCs in the treatment of ARDS and the safety and challenges of MSC therapy, highlighting key elements related to the therapeutic applications of MSCs in patients with ARDS.

Characteristics and Identification of MSCs

MSCs were initially obtained from the bone marrow, as first documented in the 1960s, and are plastic-adherent, nonphagocytic, and fibroblastic.[27] They are non-hemopoietic stromal cells that express specific cell surface markers, and can differentiate into osteoblasts, adipocytes, chondroblasts, myocytes, and neurons in vitro.[28] It was eventually found that MSCs can be obtained from most types of mesenchymal tissue, with one of the main sources being the bone marrow. Without biomarkers available for the identification of MSCs, the International Society for Cellular Therapy (ISCT) proposed the following criteria to define human MSCs: (i) a type of plastic-adherent cell under standard tissue culture conditions; (ii) expressing the cell surface markers CD105, CD73, and CD90, but not CD45, CD34, CD14, and HLA-DR; (iii) and with the capacity to differentiate into osteoblasts, adipocytes, and chondrocytes under the appropriate conditions.[29]

Concerning the biological properties, MSCs can regulate basic biological processes; exert antimicrobial and anti-inflammatory effects; and regulate cell proliferation, apoptosis, angiogenesis, or oxidative stress. MSCs also possess the capacity for self-renewal and multiple differentiation capabilities, inducing immunomodulatory effects and initiating tissue repair via the release of trophic factors, cytokines, and chemokines.[30] Because of their low tumorigenicity and short lifespan in vivo, MSCs are attractive cell-based therapeutic candidates with immunomodulatory and anti-inflammatory effects in clinical contexts.[21] Moreover, it seems that MSCs are non-immunogenic, thus, theoretically allowing for allografts without the need for immunosuppression or human leukocyte antigen matching.[31] Once harvested from the host tissue, MSCs may be rapidly proliferated ex vivo, meaning that they must be administered rapidly as a therapeutic approach after cell proliferation.[32]

MSCs can reportedly boost tissue recovery and confer anti-inflammatory, angiogenic, antifibrotic, antimicrobial, and structural reparative characteristics.[33] MSCs are low immunogenic pluripotent cells that secrete a variety of paracrine factors, including endothelial and epithelial growth factors, anti-inflammatory cytokines, and antimicrobial peptides.[21,34] In light of these specific properties, the therapeutic potential of MSCs has been investigated in the context of multiple medical and surgical conditions, including sepsis,[35] diabetes,[36] ischemic cardiomyopathy,[37] hepatic failure,[38] acute renal failure,[39] multiple sclerosis,[40] acute neurologic injuries,[41] Crohn's disease,[42] graft-versus-host disease,[43] and acute lung injury/ARDS.

Sourcing and Isolation of MSCs

Although considered an attractive approach for research and clinical applications, MSCs are far from being a uniform cell type, which makes standardization difficult. Traditionally, MSCs are harvested from the bone marrow; however, the harvesting of bone marrow-derived MSCs is a painful procedure.[44] Several other types of tissue have been identified as

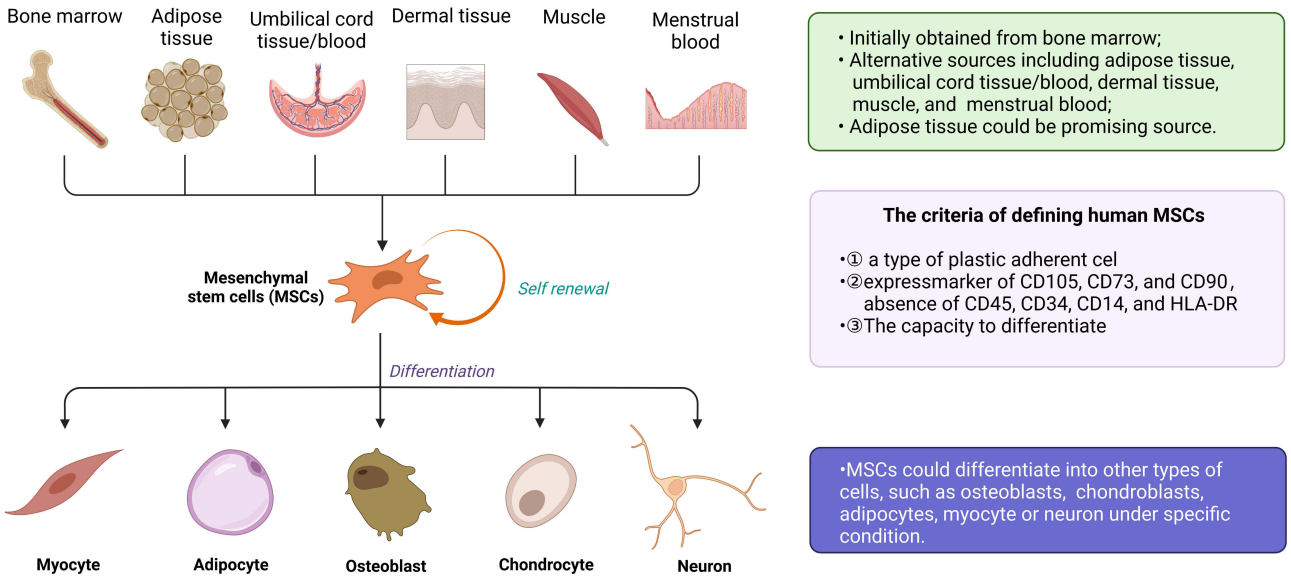

Figure 2 The sources and characteristics of mesenchymal stem cells. The criteria defining human mesenchymal stem cells: i) a plastic-adherent cell; ii) expression of CD105, CD73, and CD90, and absence of CD45, CD34, CD14, and HLA-DR; and iii) the capacity to differentiate. (Created using BioRender.com).

alternative sources of MSCs, including adipose tissue (AT), umbilical cord tissue/blood, dermal tissue, muscle, and even menstrual blood (Figure 2).[45] Regardless of the origin of the tissue, these cells conform to the ISCT classification and have been well characterized.[46] Currently, the human umbilical cord tissue (including the amnion and chorion) is the most frequently used source of MSCs given that it is a much richer source than umbilical cord blood.[47]

Notably, AT may be a more promising source of MSCs. AT is a very rich source of MSCs with ubiquitous availability; with the development of minimally invasive procedures, AT-derived-MSCs are now regarded as important candidates for autologous and allogeneic stem cell-based therapies and tissue engineering.[48] Because of the substantial and stabilized availability of AT in the body, it is the most favorable and reliable site for stem cell isolation.[49] It is estimated that AT contains over 1000 times more MSCs than the bone marrow, exhibiting a similar or even higher proliferation rate.[50,51] Furthermore, AT-derived MSCs may be easily harvested in large amounts via liposuction, which facilitates autologous transplantation.[52,53]

Although these cells have similar phenotypic and functional characteristics, MSCs from different sources have notable functional differences; isolated cells from different clonal populations can vary substantially in functional attributes,[54,55] including differences in immunogenicity and anti-inflammatory and repair abilities. Remarkably, the characteristics can also differ based on age. For example, AT-derived MSCs harvested from juveniles showed signs of greater adipogenic differentiation than those harvested from adults.[56] Another study found that MSCs harvested from ARDS models seemed to have diminished proliferation capacity, lower regenerative signals, and reduced secretion of pro/anti-inflammatory mediators.[57]

Great insights into the cell sources of MSCs have been provided by in vitro models.[58] Given their capacity to differentiate into multiple functional tissues, despite ethical or practical limitations, they are an appealing alternative to the widely used cell sources in current use.[59] However, such research remains in the initial stage and more in-depth investigation is required before these approaches can be fully utilized.

Mechanisms by Which MSCs Improve ARDS

Numerous preclinical studies have demonstrated the promise of MSCs as a potent therapeutic approach for ARDS. Based on their immediate availability, demonstrated safety, and regenerative potential, Phase 1 and 2 clinical trials have been conducted to determine the potential therapeutic application of MSC therapy in humans. It has been shown that MSCs can improve pulmonary permeability, alleviate inflammatory cell infiltration, and regulate inflammatory/anti-inflammatory mediators at different stages of disease. In summary, several mechanisms underpin MSC-based treatments

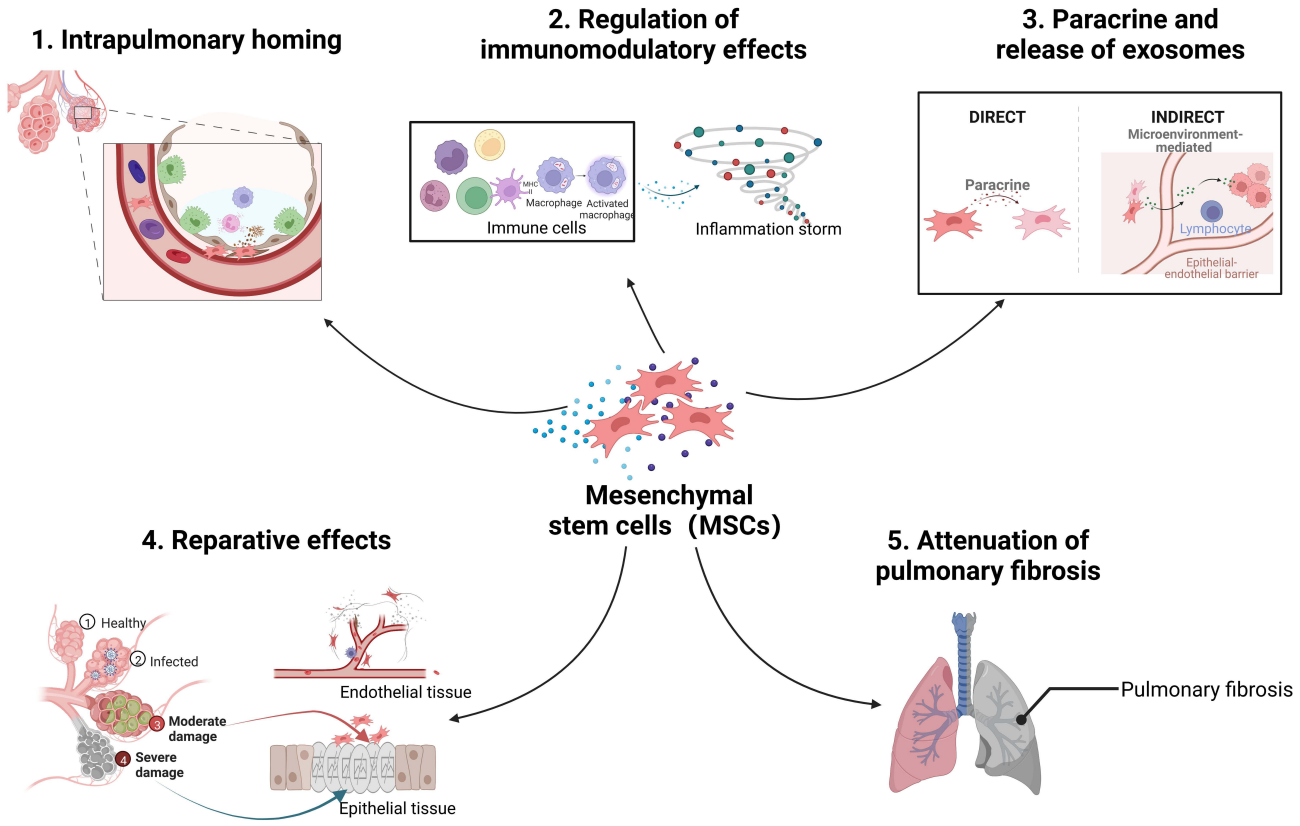

Figure 3 The mechanisms by which mesenchymal stem cell therapy improves acute respiratory distress syndrome. Several mechanisms by which mesenchymal stem cells are used to treat acute respiratory distress syndrome, including homing to the intrapulmonary injury site, regulation of immune and inflammatory cells, repair of damaged tissues, and inhibition of lung fibrosis. (Created using BioRender.com).

in ARDS, involving homing to the intrapulmonary injury site, the regulation of immune and inflammatory cells, the paracrine action of cytokines, the secretion of exosomes with benefits, and the attenuation of pulmonary fibrosis (Figure 3).

Intrapulmonary Homing

It is well recognized that MSCs can migrate to injured and affected tissue trapped in the lungs and promote tissue repair and the secretion of antimicrobial agents, cytokines, and growth factors in patients with ARDS.[22] After being injected into the body, MSCs can swiftly be "recruited" to sites of lung injury and inflammation, which is a prerequisite for stem cells to function. When the lung is damaged, necrotic cells may release a series of signaling factors to guide MSC expressing specific receptors to move and adhere to the injury site; this is considered the main stem cell homing mechanism.[60] Thereafter, various mediators, such as anti-inflammatory cytokines, angiogenic or antibacterial peptides, and extracellular vesicle particles, may be released.[18]

Regulation of Immunomodulatory Effects

The hallmark of ARDS is an acute and uncontrolled inflammatory response, and the immunomodulatory effects of MSCs involve regulation of the inflammatory response. Uncontrolled inflammation plays an essential role in the pathogenesis of ARDS, with many proinflammatory, anti-inflammatory, and immunomodulatory responses.[61] MSCs exert immunomodulatory effects via their direct contact with immune cells and the secretion of soluble factors. In patients with ARDS, the activation of inflammatory cells and the release of a series of inflammatory mediators cause epithelial and endothelial tissue damage; substantial evidence suggests that MSCs exert an anti-inflammatory effect on host tissue by secreting MSC anti-inflammatory factors, including interleukin-1ra, TSG-6, and insulin-like growth factor 1.[62–64] MSCs respond to

inflammatory stimulation and produce chemokines that recruit lymphocytes to the site of damaged tissue.[65] Furthermore, MSCs change the polarization of alveolar macrophages to an M2-like pro-resolving phenotype,[66] thus, exerting an immune regulatory function.

Paracrine Effects and Release of Exosomes with Benefits

Paracrine mechanisms affecting lung endothelial and alveolar epithelial permeability are proposed to be the major mechanism of action underlying the beneficial effects imposed by this therapeutic approach.[22,67] Paracrine factors act on surrounding cells through the interstitial space, and mechanisms involved of benefit may be depended on both paracrine release of soluble molecules associated with transfer of mitochondria and histologically active microvesicles.[68] They are widely involved in immune regulation, cell proliferation, apoptosis, endogenous progenitor cell regeneration, angiogenesis, and the release of growth factors to alter endothelial or epithelial cell injury responses during ARDS.[69,70] At present, several types of paracrine factors are thought to modulate the resolution of ARDS via four mechanisms:[71] 1) exerting anti-inflammatory effects on the host cells, 2) decreasing the permeability of the lung alveolar epithelium tissue, 3) increasing the clearance of alveolar fluid, and 4) enhancing the phagocytic activity of host mononuclear cells.

Reparative Effects

Damage to alveolar epithelial cells may lead to several injury pathways involved in the progression of ARDS, including the loss of integrity of the alveolar-capillary barrier, imbalance of alveolar fluid vector transport, and disturbance of surfactant production.[72] MSCs were found to reduce lung injury and improve survival in animal ARDS models as they could mitigate the abovementioned lung permeability, alveolar fluid carrier transport, and surfactant production dysregulation.[73] In addition, MSCs could differentiate into type I and II alveolar epithelial cells and pulmonary vascular endothelial cells in rabbits with an inhalation injury, thereby expressing their cellular markers.[74] Another study showed that the intravenous delivery of MSCs in patients with ARDS was associated with decreased alveolar permeability to protein, which may reduce pulmonary endothelial and epithelial injury.[75]

Attenuation of Pulmonary Fibrosis

Intra-alveolar and interstitial fibrosis is characteristic of late-stage ARDS and is characterized by the abnormal deposition of extracellular matrix proteins, particularly collagen. Following the development of pulmonary fibrosis, the acceleration of pulmonary dysfunction is thought to lead to ventilator dependence and aggravate the condition of a patient with ARDS.[76] Transtracheal infusion can significantly improve lung injury by attenuating ARDS interstitial fibrosis and reducing neutrophil infiltration.[77] Similarly, the intravenous infusion of MSCs was found to inhibit bleomycin-induced fibrosis in immunocompetent mice.[78]

Safety of MSCs

As a unique biological characteristic, MSCs have self-renewal and multi-directional differentiation capabilities. MSC therapy is generally considered a safe and effective method according to preclinical and clinical trials. A previous meta-analysis assessed the risk of adverse reactions linked to MSC therapy in clinical trials; by assessing acute injection-related toxicity, fever, or other adverse events in multiple organ systems, the study demonstrated the desirable safety of MSC-based therapy.[79] However, some safety issues related to the long course of treatment cannot be ignored, such as the risk of local infection, abnormal immune responses, and the excessive accumulation of amyloid-β, in particular the development of tumor induction by chromosomal abnormalities, which cannot be completely avoided based on the MSC characteristics and the effect of external conditions.[80]

Given the complicated staging of ARDS, the therapeutic window and index for MSC therapies should be further elucidated. The original and best method for assessing the effect of MSCs is intravenous administration, but this involves high doses, incurring a risk of vessel embolism. Intratracheal infusion via local administration can directly deliver cells to the site of lung injury, but the current inhalation route faces technical problems. Further, the safety of MSC therapy has been demonstrated in early-stage clinical studies based on relatively small numbers of patients. In addition, genetic

instability was observed when MSCs are cultured after several passages, which raised concerns regarding the risk of malignant proliferation or differentiation of MSCs.[81]

Sourcing of MSCs can be expanded to attain a predetermined dose in vitro and, therefore, they are not fully characterized prior to administration. As of July 2015, a total of 374 clinical trials have investigated allogeneic source derived MSCs for various indications.[82]

A single-center trial tested a single dose of 1 million adipose-derived human MSCs/kg in 12 patients with moderate to severe ARDS; the authors reported that this procedure was safe and feasible for the treatment of ARDS.[51] Another study found that a single intravenous MSC infusion of up to 10 million cells/kg predicted that body weight was well-tolerated in patients with moderate to severe ARDS without developing serious adverse events related to MSC administration after a 6-month follow-up period.[24] Subsequently, MSC-based therapy research progressed to Phase II safety trial to examine the effect of this treatment.[25,66] In these 2 years, MSCs have been administered intravenously for the treatment of patients with COVID-19-associated ARDS, with excellent results in terms of clinical tolerance and benefits on the prognosis.[83,84] For the treatment of ventilator-associated lung injury, MSCs also have certain therapeutic effects. These results are mainly focused on bronchopulmonary dysplasia that develops in premature newborns in clinical trials.[85,86] However, the therapeutic effects or mechanisms involved in the clinical setting should be further explored.

These data provide intensive care medicine researchers with additional evidence to progress to the second phase of the trial to assess the efficacy and safety of MSCs in the treatment of ARDS.

Challenges

Despite remarkable hope for the utility of MSCs in the treatment of ARDS, there remain many challenges to be addressed before their routine use in clinical practice. An initial problem is the high demand for MSCs. Bone marrow is the prevailing source of MSCs, but the number of obtained cells remains limited, and the invasive harvesting procedure is painful for healthy donors.[87] Bone marrow-derived MSCs from patients with ARDS exert immunomodulatory effects, which affect the potential application of an autologous transplantation.[88] Another study found that MSCs derived from unhealthy donors may have negative clinical outcomes when therapeutically administered.[89] Furthermore, it remains unclear which cell sources result in superior therapeutic effects in the treatment of ARDS.[90] The function of MSCs may vary depending on the culture conditions, number of passages, culture surface and hardness, and other factors. Even the same bone marrow aspirate in different clonal populations of MSCs could vary substantially in functional attributes.[91] Therefore, it is necessary to ensure product quality via titer determination, which is the primary means to ensure the quality, purity, potency, and stability of clinical research products.

Second, the dose of cell therapy is critical for the clinical treatment of ARDS using MSCs. To date, the optimal dosing regimen for the clinical administration of MSCs has not been determined. Dose-dependent effects have been confirmed in preclinical models of ARDS.[92,93] In experimental models, a single dose of MSC administration ranges from 5×10^4 to 3.6×10^7 cells;[94] in the clinical setting, the dose ranges from 2×10^6 to 1.44×10^9 cells/kg, corresponding to a 25-g mouse, which results in key challenges for harvesting such quantities. In clinical trials, doses of up to 10×10^6 cells were well tolerated and no infusion-related toxicity was observed.[24] In addition, better therapeutic benefits can be achieved by administering more than one dose, which remains challenging.

Another safety consideration potentially associated with transplants is linked to the survival and proliferation of cell populations, including immune compatibility, tumorigenicity, occlusion in microvasculature,[95] and infectious transmission. Currently, most administrations are intravenous, but issues remain regarding the high consumption for a single dose and risk of vascular embolism. Further, the therapeutic efficacy is limited by the low mobilization of MSCs to the sites of injury and their poor survival rate in the injured tissues, representing major barriers to clinical translation.

A newly-evolving concept suggests that MSCs quickly undergo apoptosis, autophagy, or efferocytosis following systemic administration, as well as potentially after intratracheal administration;[27,96] no differences were reported compared with intravenous administration.[97] Theoretically, the endotracheal infusion of MSCs is the most beneficial to epithelial cells, while intravenous infusion may be more beneficial to endothelial cells. However, the optimal route of MSC administration in ARDS may be intravenous infusion. The efficacy of different delivery routes should be evaluated to determine the best injection route before preclinical experiments or clinical trials.

Furthermore, the storage of MSCs may interfere with their gene expression or activity. The cryopreservation of allogeneic MSC therapies facilitates the availability of "off-the-shelf" products that are necessary for timely MSC administration in critical patients.[98] Cell-free alternatives of extracellular vesicles derived from MSCs, such as microvesicles, nanovesicles, and exosomes, provide alternatives to MSCs and exploit their therapeutic properties.[99–101] These strategies provide opportunities for the clinical development of MSCs and MSC-derived products with enhanced therapeutic efficacy.[102] Therefore, the premise of MSCs is to improve the ability of bone marrow MSCs to treat ARDS.

Multiple studies have recognized that characterization, identification, and optimization of lung microenvironment would be beneficial for the efficacy of MSCs in the treatment of ARDS.[103,104] For example, MSCs exposed to the bronchoalveolar lavage fluid (BALF) of patients with ARDS were blunted, and the expression of genes and proteins associated with self- vs non-self-recognition increased following exposure to the BALF of healthy individuals.[105] The latter emphasizes that MSCs should be considered when using stem cell-based therapy in ARDS cases interacting with the intrapulmonary microenvironment.[106]

Finally, the clinical development of MSC-based therapies has been relatively slow by virtue of ethical and legal restrictions.[107] Current stem cell therapies are mainly based on allogeneic therapy, and, thus, the research and clinical applications involve social ethical considerations. Treatment applications should be carried out in the context of well-designed case-controlled clinical trials consisting of rigorous, ethical, and highly regulated production processes, obtaining permission from the appropriate authorities to access mechanical information where feasible.

Conclusion

Currently, MSC therapy is a promising breakthrough in the active management of ARDS through preclinical studies and clinical trials; it may improve lung permeability, reduce inflammatory cell infiltration, down-regulate inflammatory mediators, and up-regulate anti-inflammatory mediators. Because of the spread of and damage caused by COVID-19, stem cell therapy has again garnered substantial attention, particularly as feasible drug therapies are scarce. A much better understanding of the biological and genetic characteristics of MSCs may pave the way for improved targeted therapies. Future preclinical and clinical trials are essential for assessing and optimizing the treatment to best cope with ongoing challenges in translational MSC research.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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