stem cell research&therapy

REVIEW

Therapeutic implications of mesenchymal stem cells in acute lung injury/acute respiratory distress syndrome

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Abstract

Acute lung injury (ALI), and its more severe form, acute respiratory distress syndrome (ARDS), are syndromes of acute hypoxemic respiratory failure resulting from a variety of direct and indirect injuries to the gas exchange parenchyma of the lungs. Current treatment of ALI/ARDS is primarily supportive, with lung protective ventilation and fluid conserving strategies. Despite improvement in these strategies, recent data indicate that the mortality of ALI/ARDS is still as high as 30 to 50%. Thus, there is a need for innovative therapies to further improve clinical outcomes of ALI/ARDS. Recent studies involving the administration of mesenchymal stem cells (MSCs) for the treatment of experimental ALI/ARDS have shown promising results. This review focuses on existing studies that have tested the use of MSCs in models of ALI/ARDS, and the potential mechanisms underlying their therapeutic effects.

Introduction

Acute lung injury (ALI), and its more severe form, acute respiratory distress syndrome (ARDS), are syndromes of acute hypoxemic respiratory failure resulting from a variety of direct and indirect injuries to the gas exchange parenchyma of the lungs [1,2]. Pulmonary or non-pulmonary infections with sepsis are the most common causes of ALI and ARDS, although gastric aspiration, massive transfusions, trauma and other factors contribute [1,2]. Current treatment of ALI/ARDS is primarily supportive, with lung protective ventilation and fluid conserving strategies [3-5]. Despite improvement in these strategies, recent data indicate that the mortality of ALI/ARDS is still as high as 30 to 50% [1,6]. Thus, there is a need for innovative therapies to further improve clinical outcomes of ALI/ARDS. Although it is a controversial field, some studies have demonstrated that bone marrow-derived mesenchymal stem cells (MSCs) can localize to and/or participate in the development of new lung tissue during the past few years [7,8]. In addition, MSC transfer has been attempted as a therapeutic strategy in experimental lung injury. Recent studies involving the administration of MSCs for the treatment of experimental ALI/ARDS have shown promising results [9-11]. This review focuses on existing studies that have tested the use of MSCs in models of ALI/ARDS, and the potential mechanisms underlying their therapeutic effects.

Mesenchymal stem cells

MSCs, also named marrow stromal stem cells, were first identified in 1968 by Friedenstein and colleagues [12]. Because there are no MSC-specific cell surface markers, the International Society of Cellular Therapy defined MSCs by the following three criteria in 2006: 1) MSCs must be adherent to plastic under standard tissue culture conditions; 2) MSCs must express certain cell surface markers, such as CD105, CD90 and CD73, but must not express other markers, including CD45, CD34, CD14 or CD11b; and 3) MSCs must have the capacity to differentiate into mesenchymal lineages, including osteoblasts, adipocytes and chrondoblasts, under *in vitro* conditions [13].

MSCs have now been isolated from a wide variety of tissues, including umbilical cord blood, Wharton's jelly, placenta, adipose and lung tissue [14-18]. Numerous studies have demonstrated that MSCs have a high degree

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of plasticity, as they differentiate into a variety of cell lineages, including fibroblasts, myofibroblasts, osteoblasts, chondroblasts, adipocytes, myoblasts, and epithelial cells [19,20]. MSCs do not possess the plasticity of embryonic stem cells, but they offer practical advantages because of their ease of isolation and propagation and also because their use does not involve the ethical issues often raised by the use of embryonic stem cells [21]. Several experimental studies have indicated that MSCs may have potential therapeutic application in clinical disorders, including myocardial infarction, diabetes, hepatic failure, and acute renal failure [22-25]. Experimental studies have also provided evidence indicating that MSCs may be useful for the treatment of ALI/ARDS [26] (Table 1).

Mechanisms of action of mesenchymal stem cells in the treatment of acute lung injury/acute respiratory distress syndrome

The management of ALI/ARDS with MSCs is suggested to involve two different mechanisms: a cell engraftment mechanism and a paracrine/endocrine mechanism.

Cell engraftment mechanism

Early studies suggest that engraftment plays an important role in MSC therapy of ALL/ARDS. Krause and colleagues [27] found that a single bone marrow-derived cell could give rise to cells of multiple different organs, including the lung. They reported up to 20% engraftment of bone marrow-derived cells in the lung, including epithelial cells, from a single hematopoietic precursor. Ortiz and colleagues [28] systemically administered MSCs purified by immunodepletion from male bleomycin-resistant BALB/c mice into female bleomycin-sensitive C57BL/6 recipients. Fluorescence *in situ* hybridization revealed that engrafted male cells were localized to areas of bleomycin-induced injury and exhibited an epithelium-like morphology. Moreover, purification of type II epithelial cells from the lungs of transplant recipients resulted in a three-fold enrichment of male, donor-derived cells as compared with whole lung tissue. Rojas and colleagues [29] administered bleomycin to mice with or without preceding busulfan-induced myelosuppression. They found that myelosupression increased susceptibility to bleomycin-induced lung injury and that

Table 1 Therapeutics role of MSCs in the pre-clinical models of ALI/ARDS

MSC delivery route	Lung injury model	Mechanism of therapy	Reference
IV delivery immediately post-injury	Murine IT bleomycin-induced ALI	Engrafted male cells were localized to areas of bleomycin-induced injury and exhibited an epithelium-like morphology	[28]
		Reduced the degree of bleomycin-induced inflammation and collagen deposition within lung tissue	
IV delivery 6 h post-injury	Murine IT bleomycin-induced ALI	Differentiation of engrafted BMDMSC into specific and distinct lung cell phenotypes	[29]
		An increase in circulating levels of G-CSF and GM-CSF and with a decrease in inflammatory cytokines	
IT delivery 4 h and 24 h post-injury	Murine IT LPS-induced ALI	Significant decrease in excess lung water, pulmonary edema, bronchoalveolar lavage protein, endothelial and alveolar epithelial permeability	[35]
IT delivery 1 h and 24 h post-injury	Endotoxin-induced ALI in *ex vivo* perfused human lung	Secretion of KGF by mesenchymal stem cells resulting in improved endothelial permeability and restoration of alveolar epithelium fluid transport	[36]
IV delivery immediately post-injury	Murine IT bleomycin-induced ALI	Secretion of IL-1 receptor antagonist	[37]
		Inhibition of TNF-α production by macrophage and IL-1a-dependent T cell line	
IV delivery 1 h and 24 h post-injury	Murine IP LPS-induced ALI	Prevented endotoxin-induced lung inflammation, injury, and edema	[39]
		Suppressed the endotoxin-induced increase in circulating pro-inflammatory cytokines without decreasing circulating levels of anti-inflammatory mediators	
IV delivery immediately post-injury	Murine IT bleomycin-induced ALI	Promoted Th1 phenotype and inhibited Th2-mediated allergic airways inflammation	[44]
IT delivery 4 h post-injury	Murine IT LPS-induced ALI	Diminished levels of alveolar CD4 + CD25 + Foxp3 + T_{reg} and balancing anti- and pro-inflammatory factors	[46]
IV delivery 6 h and 24 h post-injury	Murine CLP-induced ALI	Modification of inflammatory gene transcriptional activity	[48]
		Downregulation of the acute inflammatory response and upregulation of pathways relevant to phagocytosis and bacterial clearance	
IT delivery 4 h and 24 h post-injury	*E. coli* pneumonia-induced ALI	Secretion of the anti-microbial peptide LL-37 resulting in increased bacterial clearance	[49]

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BMDMSC, bone marrow-derived mesenchymal stem cell; CLP, cecal ligation and puncture; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IP, intraperitoneal; IT, intratracheal; IV, intravenous; KGF, keratinocyte growth factor; LPS, lipopolysaccharide; MSC, mesenchymal stem cell.

bone marrow-derived MSC transfer was protective. Protection was associated with the differentiation of engrafted MSCs into specific and distinct lung cell phenotypes. However, these results were questioned by multiple groups, who observed only engraftment of leukocyte lineages [30] or observed low engraftment rates in lung injury models of <1% [31]. A variety of animal models, method of injury and route of delivery may account for the different results. Lee and colleagues [26] found different mechanisms for two different research models of MSC therapy. In the same study group, the authors suggested the intravenous route might be the preferred approach compared with the intra-alveolar route [32]. Results from these studies demonstrate that the role of cell engraftment needs to be researched further [33].

Despite initial interest in their multipotent properties, engraftment in the lung now does not appear to be a key mechanism of action for many MSCs. The beneficial effect of MSCs appears to derive more from their capacity to home to injured tissue beds, interact with injured host cells, and secrete paracrine soluble factors that modulate immune responses as well as alter the responses of endothelium or epithelium to injury through the release of growth factors and antimicrobial peptides [26].

Paracrine/endocrine mechanism

Much current interest in MSCs has focused on soluble factors due to their ability to secrete multiple paracrine factors such as growth factors, factors regulating endothelial and epithelial permeability, factors regulating innate and adaptive immunity, anti-inflammatory cytokines, and, more recently, antimicrobial peptides that can potentially treat the major abnormalities that underlie ALI/ARDS, including impaired alveolar fluid clearance, altered lung endothelial permeability, dysregulated inflammation, and infection.

A number of groups have reported that MSCs can release several growth factors and regulate endothelial and epithelial permeability, as well as enhance repair. Mei and colleagues [34] delivered syngeneic MSCs with or without transfection with plasmid containing the human *ANGPT1* gene (pANGPT1) into mice 30 minutes after intratracheal instillation of lipopolysaccharide (LPS) to induce lung injury. Administration of MSCs significantly reduced LPS-induced pulmonary inflammation. MSCs transfected with pANGPT1 nearly completely reversed the LPS-induced increase in lung permeability.Histological analysis confirmed a marked decrease in inflammatory infiltrates, interalveolar septal thickening, and interstitial edema. Gupta and colleagues [35] tested the effects of bone marrow-derived MSCs in a mouse model of severe lung injury. They administered endotoxin by the intrapulmonary route (5 mg/kg), which was followed by MSCs 4 hours later (750,000 cells) by the intratracheal route. MSCs reduced the severity of lung injury as measured by excess lung water, wet-to-dry ratio, and bronchoalveolar lavage (BAL) protein concentration. There was also a significant decrease in excess lung water, a measure of pulmonary edema, and BAL protein, a measure of endothelial and alveolar epithelial permeability, in the MSC-treated mice. Lee and colleagues [36] explored the therapeutic capacity of human MSCs to restore alveolar epithelial fluid transport and lung fluid balance from ALI in an *ex vivo* perfused human lung preparation injured by endotoxin. Treatment with allogeneic human MSCs or its conditioned medium given 1 hour following endotoxin-induced lung injury reduced extravascular lung water, improved lung endothelial barrier permeability and restored alveolar fluid clearance. Using small interfering RNA knockdown of potential paracrine soluble factors, secretion of keratinocyte growth factor (KGF) was essential for the beneficial effect of MSCs on alveolar epithelial fluid transport, in part by restoring amiloride-dependent sodium transport. They concluded that treatment with allogeneic human MSCs or the conditioned medium restored normal fluid balance in an *ex vivo* perfused human lung injured by endotoxin.

Many studies have demonstrated that MSCs also release anti-inflammatory cytokines that can dampen the severity of inflammation in ALL/ARDS. Ortiz and colleagues [28] isolated murine MSCs and administered them intravenously immediately or 7 days following bleomycin-induced lung injury. They found that MSCs improved survival and lung inflammation when administered intravenously. Mice treated with MSCs immediately following bleomycin exposure also had significantly reduced collagen deposition, and reduced expression of matrix metalloproteinases 2 and 9. The degree of the anti-inflammatory effects was striking in comparison to the relatively low levels of lung engraftment. In a subsequent study [37], the same authors found that there was an important contribution by a subpopulation of mouse MSCs that produced interleukin-1 receptor antagonist (IL1RN). IL1RN is a cytokine that competitively competes with IL-1β for IL-1 receptor binding. IL-1β is one of the major inflammatory cytokines in pulmonary edema fluid in patients with ALI/ARDS [38]. In a model of acute lung injury by intratracheal endotoxin in mice, Gupta and colleagues [35] reported that intratracheal MSCs reduced BAL levels of the pro-inflammatory cytokines TNF-α and macrophage inflammatory protein (MIP)-2 as well as plasma levels of MIP-2. There was a corresponding increase in the anti-inflammatory cytokines IL-10, IL1RN, and IL-13. Xu and colleagues [39] injected C57BL/6 mice intraperitoneally with 1 mg/kg endotoxin followed by intravenous infusion of MSCs. MSC administration prevented endotoxin-induced lung inflammation, injury, and edema. It also suppressed the endotoxin-induced increase in circulating pro-inflammatory cytokines, including IFN-γ, IL-1β, MIP1-α, and KC (murine homolog of IL-8), without

decreasing circulating levels of anti-inflammatory mediators. *Ex vivo* co-cultures of MSCs and lung cells from endotoxemic animals demonstrated a bilateral conversation in which lung cells stimulated proliferation and migration of stem cells and suppressed pro-inflammatory cytokine production by lung cells. They concluded that MSCs decrease both the systemic and local inflammatory responses induced by endotoxin. Curley and colleagues [40] determined the potential for MSCs to enhance repair after ventilator-induced lung injury (VILI). MSC therapy enhanced repair following VILI and attenuated alveolar TNF-α concentrations while increasing concentrations of IL-10. The beneficial effect of the MSC secretome on repair of pulmonary epithelial wounds was attenuated by prior depletion of KGF. The authors demonstrated that MSC therapy enhances lung repair following VILI via a paracrine mechanism that may be KGF-dependent.

Recently, MSCs have been shown to possess immunomodulatory properties. These include suppression of T-cell proliferation, influencing of dendritic cell maturation and function, suppression of B-cell proliferation and terminal differentiation, and immune modulation of other immune cells such as natural killer cells and macrophages [41-43]. Immunomodulation is another important aspect of the paracrine/endocrine mechanism. Jun and colleagues [44] found that lung MSCs could attenuate the bleomycin-associated pathology and mitigate the development of pulmonary arterial hypertension. Lung MSCs modulated a decrease in numbers of lymphocytes and granulocytes in BAL and demonstrated an inhibition of effector T-cell proliferation *in vitro*. Goodwin and colleagues [45] ascertained the effects of systemic administration of MSCs in a mouse model of Th2-mediated allergic airways inflammation. Ovalbumin (OVA)-induced allergic airways inflammation was induced in wild-type C57BL/6 and BALB/c mice as well as in IFNγ receptor null mice. Both syngeneic and allogeneic MSCs inhibited airways hyper-reactivity and lung inflammation through a mechanism partly dependent on IFNγ. MSCs promoted Th1 phenotype *in vivo* as assessed by both OVA-specific CD4 T lymphocyte cytokine production and OVA-specific circulating immunoglobulins. MSCs inhibit Th2-mediated allergic airways inflammation by influencing antigen-specific CD4 T lymphocyte differentiation. Promotion of a Th1 phenotype in antigen-specific CD4 T lymphocytes by MSCs is sufficient to inhibit Th2-mediated allergic airways inflammation through an IFNγ-dependent process. Sun and colleagues [46] recently reported that transplantation of MSCs ameliorated ALI by enhancing the diminished levels of alveolar CD4 + CD25+ Foxp3 + T_{reg} and balancing anti- and pro-inflammatory factors in ALI mice. Recent evidence has shown that MSCs can act as an immunostimulatory cell [47]. Their complex function and role in the treatment of ALL/ARDS needs further research.

Recently, some studies found that MSCs have antimicrobial effects through soluble factors. Mei and colleagues [48] evaluated the therapeutic effect of MSCs on a polymicrobial model of sepsis. Sepsis was induced in C57Bl/6J mice by cecal ligation and puncture (CLP), followed 6 hours later by an intravenous injection of MSCs or saline. Twenty-eight hours after CLP, plasma, BAL fluid and tissues were collected for analyses. Bacterial burden was assessed by determining the number of colony forming units (CFUs) in the spleens of saline- or MSC-treated mice. Bacterial CFU counts were high in the spleens of mice that had undergone CLP. Treatment with MSCs significantly reduced CFU counts at 28 hours after CLP, suggesting that MSCs directly or indirectly modulate the ability of the host's phagocytes to clear bacterial infection or participate in bacteria clearance. Although the exact mechanism of increased phagocytosis is not known, the expression microarray analysis performed in this study revealed upregulation of pathways associated with monocyte/macrophage phagocytosis, natural killer cell activity, and antigen presentation.

Krasnodembskaya and colleagues [49] studied the effect of human MSCs derived from bone marrow on the bacterial growth of Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus*) bacteria. MSCs as well as their conditioned medium demonstrated marked inhibition of bacterial growth in comparison with control medium or normal human lung fibroblasts. Analysis of expression of major antimicrobial peptides indicated that one of the factors responsible for the antimicrobial activity of MSC-conditioned medium against Gram-negative bacteria was the human cathelicidin antimicrobial peptide, hCAP-18/LL-37. Both mRNA and protein expression data showed that the expression of LL-37 in MSCs increased after bacterial challenge. Using an *in vivo* mouse model of *E. coli* pneumonia, intratracheal administration of MSCs reduced bacterial growth in the lung homogenates and in the BAL, and administration of MSCs simultaneously with a neutralizing antibody to LL-37 resulted in a decrease in bacterial clearance. In addition, the BAL itself from MSC-treated mice had a greater antimicrobial activity in comparison with the BAL of phosphate-buffered saline-treated mice. Taken together, the results suggest that MSCs exert both direct effects on bacteria and positively modulate the host's phagocytic capacity.

Gupta and colleagues [50] found that treatment with MSCs enhanced bacterial clearance from the alveolar space of the *E. coli*-induced pneumonia mouse model as early as 4 hours after instillation. This reduction in bacterial burden persisted at 24 hours when the number of *E. coli* in the whole lung homogenate was measured in MSC-treated and control mice. MSCs significantly upregulate their production of lipocalin 2 in response to LPS and inflammatory mediators generated by activated

macrophages, and this response contributes to the antibacterial effect observed with MSC treatment. In the study of Kim and colleagues [51], ALI was induced by intratracheal *E. coli* instillation, 3 hours after which MSCs, fibroblasts or phosphate-buffered saline were intratracheally administered randomly and survival was analyzed for 7 days post-injury. MSC transplantation increased survival and attenuated lung injuries in ALI mice. MSCs reduced the elevated lung water content at day 3 post-injury and bacterial counts in blood and BAL on day 7 post-injury. Enhancing bacterial clearance is one of the mechanisms of treatment.

Conclusion

ALI/ARDS is the most common cause of hypoxemic respiratory failure in critically ill patients. Current treatment for ALI/ARDS is supportive and therefore new treatments are needed. MSCs are adult stem cells most commonly isolated from the bone marrow that possess unique immunomodulatory and paracrine properties that make them attractive for cell-based therapy. Although initial research on MSCs was focused on the possibility that cell-based therapy with MSCs could provide a mechanism to replace injured lung epithelium, subsequent studies in the mature and the immature lung have focused more on the paracrine/endocrine properties of MSCs, which have value in limiting lung injury and enhancing lung repair. Given the promising initial results obtained with the use of MSCs in experimental models of ALI/ARDS, there has been enthusiasm to advance cell-based therapy to patients with ALI/ARDS. While clinical trials of MSC-based therapy have been initiated in patients with cardiac, renal and auto-immune diseases, there are several questions that need to be addressed before cell-based therapy can be tested in patients with ALI/ARDS. Currently, the following four properties are considered the most important: the ability to home to sites of inflammation following tissue injury when injected intravenously; the ability to differentiate into various cell types; the ability to secrete multiple bioactive molecules capable of stimulating recovery of injured cells and inhibiting inflammation; the lack of immunogenicity and the ability to perform immunomodulatory functions [52]. Although clinical trials of MSCs in human subjects, to date, have not reported adverse immune side effects [53,54], future research in this field should continue and focus on elucidating the basic mechanisms responsible for the beneficial effects of MSCs, as well as negatives that are associated with the possible use of MSCs to treat ALL/ARDS patients. In the process, a novel therapy for ALI/ARDS might emerge.

Abbreviations

ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; BAL: Bronchoalveolar lavage; CFU: Colony forming unit; CLP: Cecal ligation and puncture; IFN: Interferon; IL: Interleukin; IL1RN: Interleukin-1 receptor antagonist; KGF: Keratinocyte growth factor; LPS: Lipopolysaccharide; MIP: Macrophage inflammatory protein; MSC: Mesenchymal stem cell; OVA: Ovalbumin; TNF: Tumor necrosis factor; VILI: Ventilator-induced lung injury.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YYW wrote the manuscript. YYW, XZL, and LBW assisted with the revision of English grammar and style. All authors discussed the content and approved the final version of manuscript.

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