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Review Article

Mesenchymal stromal cell-based therapy in lung diseases; from research to clinic

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Abstract: Recent studies demonstrated that mesenchymal stem cells (MSCs) are important for the cell-based therapy of diseased or injured lung due to their immunomodulatory and regenerative properties as well as limited side effects in experimental animal models. Preclinical studies have shown that MSCs have also a remarkable effect on the immune cells, which play major roles in the pathogenesis of multiple lung diseases, by modulating their activity, proliferation, and functions. In addition, MSCs can inhibit both the infiltrated immune cells and detrimental immune responses in the lung and can be used in treating lung diseases caused by a virus infection such as Tuberculosis and SARS-COV-2. Moreover, MSCs are a source for alveolar epithelial cells such as type 2 (AT2) cells. These MSC-derived functional AT2-like cells can be used to treat and diminish serious lung disorders, including acute lung injury, asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis in animal models. As an alternative MSC-based therapy, extracellular vesicles that are derived from MSC-derived can be employed in regenerative medicine. Herein, we discussed the key research findings from recent clinical and preclinical studies on the functions of MSCs in treating some common and well-studied lung diseases. We also discussed the mechanisms underlying MSC-based therapy of well-studied lung diseases, and the recent employment of MSCs in both the attenuation of lung injury/inflammation and promotion of the regeneration of lung alveolar cells after injury. Finally, we described the role of MSC-based therapy in treating major pulmonary diseases such as pneumonia, COPD, asthma, and idiopathic pulmonary fibrosis (IPF).

Keywords: Mesenchymal stromal cell, lung, asthma, ARDS, pneumonia, IPF

Introduction

Mesenchymal stromal cells (MSCs) are widely distributed and multipotent cell populations that can self-renew and are commonly used in a wide range of clinical trials (**Table 1**) for cell-based therapies because of their ability to regenerate. Moreover, MSC therapeutic potentials are due to the ability of MSCs to differentiate into many different types of cells, their rapid proliferation in vitro, and their reduced immunogenicity and their ability to secrete several biological elements that can be used for tissue repair and regeneration [1]. Although MSCs have low immunogenicity in co-culture systems in vitro, they can still trigger immune response. In addition, MSCs are reactive to changes in oxygen concentration, pH value and other changes in the microenvironment by producing several trophic and immune-modulatory factors that have a major role in tissue repair and regeneration. MSCs can be isolated from multiple sources and used in preclinical and clinical applications [2-5]. The commonly used methods for MSCs extraction were summarized by Hao et al [6].

Several tissues, organs, and fluids such as the bone marrow, amniotic fluid, adipose tissue, placenta, umbilical cord blood, skin and lung can be used for isolation of MSCs [7]. These characteristic features made MSCs a major cell type in the repair and regeneration of diseased lungs [8]. MSCs gown in culture can suppress immune responses and both differentiate and give rise to alveolar epithelial type II cells (AT2) [8, 9]. In addition, MSC ability to both mediate tissue regeneration and suppress inflammation

Table 1. Summary of recent human MSC therapeutic clinical trials

ClinicalTrials.gov Identifier	Condition or disease	Intervention/treatment	Actual Enrollment	Primary endpoint	Primary Outcome Measures
NCT03137199	Asthma	Allogenic Human Mesenchymal Stromal Cells (hMSCs)	3 participants	Week 4 post infusion	Number of Participant with treatment emergent serious adverse events
NCT02192736	Asthma	Trophic factors from umbilical cord mesenchymal stromal cells	20 participants	1 month	Number of patients with adverse events
NCT01902082	Acute respiratory distress syndrome (ARDS)	Allogeneic adipose-derived MSCs	20 participants	From day 0 at the start of treatment to day 28	Compare the adverse events between mesenchymal stromal cell treatment and placebo groups
NCT01385644	Idiopathic Pulmonary Fibrosis (IPF)	Placental Mesenchymal Stromal Cells (MSC)	8 patients	6 months post MSC infusion	Percentage Change in Lung Function as Assessed by FVC Compared to Baseline
NCT02013700	Idiopathic Pulmonary Fibrosis (IPF)	Allogeneic Adult Human Mesenchymal Stromal Cells (hMSCs)	9 participants	One month post infusion	Incidence of any treatment-emergent serious adverse events (TE-SAEs)
NCT01919827	Idiopathic Pulmonary Fibrosis (IPF)	Autologous mesenchymal stromal cells derived from bone marrow	17 patients	Up to 12 months	Number of participants with adverse side effects

is the basis for their application in treating several major respiratory disorders and diseases such as idiopathic pulmonary fibrosis (IPF), asthma, chronic obstructive pulmonary disease (COPD), and acute respiratory distress syndrome (ARDS) [10-14]. Although MSCs have shown first promising clinical results in lung injury (e.g., IPF, COPD, ALI/ARDS/COVID19), there is still limitations considering optimal effective clinical use at least partially due to their low MSC engraftment for several reasons. For example, MSCs have a short-lived viability after injection and many MSCs can be trapped in the lungs, after transplantation, which reduces MSC populations that occupy the target sites.

The migration of bone marrow-derived mesenchymal stromal cells (BM-MSCs) into injured tissue is regulated by mechanical and chemical factors, including chemokines, cytokines, and growth factors [15]. Both in vivo and in vitro experiments [16] have confirmed the immunoregulatory effects of MSCs which are induced by INF-γ and mediated by cell-to-cell contract and soluble factors [17].

Due to their potent anti-inflammatory and immunosuppressive effects, MSCs have clear clinical implications in pulmonary diseases. Many recent clinical and research studies suggest that MSCs are a promising approach for treating several common lung diseases. Therefore, the goal of this article is to review and discuss the key research findings on the functions of MSCs in the treatment of common lung diseases from recent clinical and preclinical studies. We expanded our discussion in this article to include the mechanisms underlying MSC-based therapy of well-studied lung diseases. Moreover, we reviewed the recent employment of MSCs in both the attenuation of lung injury/inflammation and promotion of the regeneration of lung alveolar cells after injury. Furthermore, we described the role of MSC-based therapy in treating major pulmonary diseases such as pneumonia, ARDS, COPD, asthma, and fibrosis.

Mechanisms of MSC treatment of lung disorders

MSCs have a major contribution to multiple lung disorders. MSCs can regulate the activity, function, and proliferation of several immune cells, including neutrophils, regulatory and effector T cells, macrophages, and dendritic cells (DCs), which are involved in the pathogenesis of multiple inflammatory pulmonary disorders. Remarkably, MSCs can exert their effects by changing the immune responses using juxtracrine or paracrine mechanisms [18] and/or rendering T lymphocytes that express CD4 (e.g., Th17, Th2, and Th1 cells) anergic. Interestingly, the interactions between the inhibitory molecule programmed death 1 (PD-1) and its ligands (PD-L1 and PD-L2) play an important role in MSC-mediated inhibition of the proliferation of T cells [8]. In addition, MSCs can suppress B-cell proliferation and IgG secretion by producing the anti-inflammatory cytokines transforming growth factor beta (TGF-β) and interleukin 10 (IL-10), while increasing immunosuppressive T-regulatory cells.

MSCs can inhibit abnormally activated Th1 cells, restore the Th1/Th2 balance and suppress the activity of cytotoxic CD8+ T lymphocytes via the NKG2D pathway [19]. Transplanted MSCs can remarkably reduce the total number of effector T cells by both affecting T lymphocytes (e.g., Th17-, Th2-, or Th1)-dependent inflammation and the expression of IL-10 cytokine. MSC can mediate these effects by suppressing cyclin-D2, but increasing the expression of cyclin-dependent kinase inhibitor (p27-kip1) in T cells, which cross-talk with MSCs [8]. A notable in vitro study demonstrated that dental follicle mesenchymal stromal cells (DF-MSCs) could suppressed proliferation of CD4+ T lymphocytes by increasing the number of FoxP3 expressing CD4+CD25+ T regulatory cells [20].

MSCs can also inhibit T cell-dependent inflammation by secreting several signaling molecules and factors, including TGF-β, nitric oxide (NO), hepatocyte growth factor (HGF), immunosuppressive factors such as prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO) and IL-10 [21]. MSC-derived TGF-β inhibits the interleukin 2 (IL-2)-induced activation of Jak-Stat pathway in T cells and is required for arresting the T cell cycle at G1 phase [22], while nitric oxide (NO) derived from MSCs can affect T cells by reducing STAT5 (signal transducer and activator of transcription 5) phosphorylation, leading to the arrest of T cell cycle [21]. The role of MSC-derived IDO is to promote the degradation

of tryptophan to kynurenine, which stimulates T cell apoptosis or suppress the clonal expansion of T cells [23], whereas PGE2 derived from MSCs functions to either attenuate the expression of IL-2 receptors, JAK-3 which modify the responsiveness of T cells to IL-2 or inhibit on IL-2 production [24].

MSCs can regulate the antigen-presenting functions of DCs that is dependent on the activity of PGE2 and cytokines such as IL-10 and IL-6, in addition to their suppression of effector T cells. This regulatory effect of MSCs can eventually suppress the generation of several T lymphocytes (e.g., Th17, Th2, and Th11 cells) [8]. The MSC-DC interactions via IL-6 leads to immaturity of DCs as evidenced by a characteristic decrease in their antigen-presenting capacity because of both reduced expression of the major histocompatibility complex (MHC) and failure of subsequent activation of Th1 [25]. In addition, the interactions between the dendritic cells (DCs) and MSCs can result in stimulating DC tolerogenic phenotype and inducing the polarization of inflammatory M1 macrophages to immunosuppressive M2 macrophages, which can promote the production of certain anti-inflammatory factors such as IL-10 cytokine and TGF-β growth factor. These changes can enhance tissue repair/regeneration and downregulate the secretion of several inflammatory factors and cytokines, including IL-1β, tumor necrosis factor alpha (TNF-α), IL-12, and tumor necrosis factor, in both macrophage and DC cells [1, 3, 8, 26-28].

Interestingly, the tolerogenic DCs and M2 macrophage cells can induce the secretion of MSC-derived immunosuppressing human leucocyte antigen- (HLA-) G5. The later antigen can suppress allogeneic T-cell proliferation but increase the generation of T regulatory cells (Tregs) that is dependent on the activity of IL-10 cytokine and TGF-β growth factor [29]. In addition, TGF-β1 can promote M2 macrophage polarization through the miR-132/Mycbp2/TSC2 axis [30]. These changes could help create an appropriate anti-inflammatory microenvironment in injured lung tissues [31].

MSCs are an important source of AT2-like cells in culture. BM-MSCs can differentiate into AT2 cells that produce SP-C (surfactant protein-C) when co-cultured with normal fetal lung mesenchyme (MRC-5) cells in vitro in a medium containing different ratios of BM-MSCs to MRC-5 cells and supplement types [32]. AT2 cells can also be produced by the decidua (D), and amniotic fluid (AF) cells. Both the D and AF cells can give rise into AT2 cells in vitro that can be abbreviated based on their source into D-MSCs and AF-MSCs; respectively [9, 33]. Many signaling pathways and molecules are critical for MSC differentiation into AT2 cells, including the Wnt pathway [34, 35]. Indeed, Wnt3a can stimulate the activity of canonical Wnt/β-catenin, while Wnt5a can induce activation through non-canonical Wnt pathway in a modified co-culture system with lung epithelial-12 (MLE-12) cells. Activated Wnt signaling can stimulate the differentiation of MSCs into AT2 cells that produce surfactant protein-B (SP-B), surfactant protein-C (SP-C) and surfactant protein-D (SP-D) [34, 35]. This Wnt signaling-dependent MSC differentiation was confirmed by blocking the activity of Wnt signaling using JNK or PKC inhibitors that inhibited MSC differentiation to AT2-like cells [34, 35]. Other studies further supported these findings by demonstrating that Wnt/β-catenin pathway may regulate the differentiation of lung resident mesenchymal stromal cell (LR-MSCs) into epithelial cells [36].

Recent research further confirmed that MSCs can regulate lung inflammation and attenuate lung injuries through immune cells. MSCs overexpressing TGF-β1 have been found to modulate the balance of Th17/Treg in the lungs of ARDS mice [37], as MSCs could induce the apoptosis of activated T cells through Fas/FasL signaling pathway. In addition, in vivo study showed that MSCs can inhibit the proinflammatory function of Ly6C+ CD8+ T cells of mice models [38]. MSCs can also decrease immunoglobulin-related gene expression in lung B cells [39]. Moreover, MSCs could induce DC immune tolerance via paracrine hepatocyte growth factor [40], through activating Notch signaling [41]. Furthermore, MSCs can regulate macrophage polarization through inhibiting glycolysis in macrophages [42]. Interestingly, the use of transplanted MSCs to attenuate inflammatory pulmonary diseases is mostly dependent on their paracrine effect, with only limited report confirming MSC-derived regeneration in vivo model (rabbit mandibles) [43], suggesting the function of MSC rely more on physiological conditions.

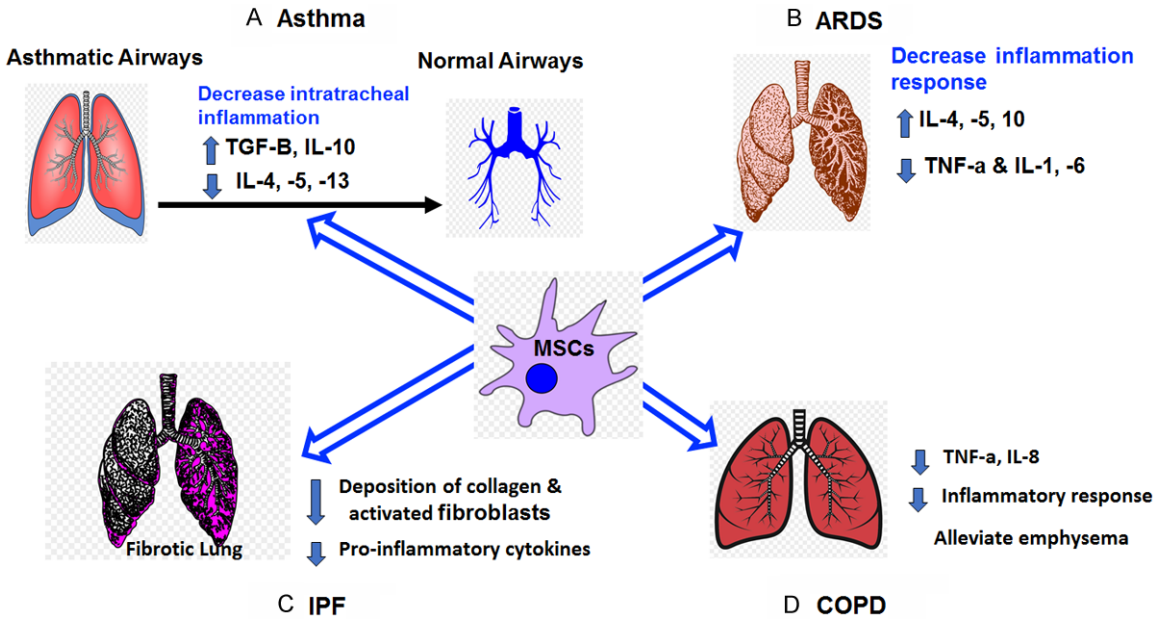

Figure 1. Summary of the major functions of MSCs in key lung diseases and disorders. A. MSC treatment for asthma can increase TGF-beta and IL-10, but decrease the cytokines IL-4, IL-5 and IL-13. B. ARDS treatment with MSCs can lead to the increase of IL-4, IL-5, and IL-10, but decreases TNF-alpha, IL-1, and IL-6. C. MSC treatment for the IPF leads to the reduction of the deposition of collagen, activated fibroblasts, and pro-inflammatory cytokines. D. COPD treatment with MSCs can lead to a reduction in the TNF-alpha, IL-8 and inflammatory response, as well as the alleviation of emphysema.

MSC therapeutic potentials in treating respiratory diseases

Since the damage of the alveolar-epithelial barriers and alveolar type II (AT2) is a major characteristic feature in patients with pulmonary diseases, the application of MSCs in the treatment of respiratory diseases is a popular and interesting research topic. The following sections of the review will describe the potential of MSC-based treatments for several major pulmonary diseases.

MSC-based therapy for asthma

Asthma is a major chronic and inflammatory pulmonary disease characterized by chronic inflammation of the airways, swelling of bronchial mucosa and increased production of mucus. In response to airway inflammation, several chemokines, and inflammatory cytokines, including IL-6, IL-1β, TNF-α and IL-4, are secreted by active mast cells and basophils to facilitate the accumulation of several cell types in the lung such as circulating eosinophils, neutrophils, and CD4+ Th2 cells [44]. The active neutrophils and eosinophils can release numerous matrix-degrading enzymes and cytokines to induce bronchial hyperresponsiveness and airway remodeling by promoting bronchoconstriction, extracellular matrix deposition, and epithelial layer degradation [31, 45]. In addition, the CD4+ Th2 cells can enhance the activation of eosinophils in IL-5-dependent manner and promote hyperresponsiveness of airways as well as metaplasia of goblet cells in an IL-3-dependent manner [46] (**Figure 1**).

In vitro studies showed that MSCs can inhibit the proliferation of CD4+ Th2 cells through mature dendritic cells, reduce he activation mast cells that depends on IgE and suppress plasma cell-produced IgE [8]. In addition, in vitro co-culture studies have shown that human umbilical cord blood-derived MSCs (hUC-MSC) can directly downregulate the production of IL-5 and IL-13 from differentiated mouse Th2 cells [47]. In vivo animal studies demonstrated that MSCs can reduce inflammation by producing soluble factors, remodel pulmonary airways and rescue pulmonary functions [48-51]. In addition, MSCs display immunomodulatory effects, since dental follicle mesenchymal stromal cells (DC-MSCs) of asthmatic patients have

been found to suppress CD4+ Th2 cells proliferation via IDO pathway and inhibit IL-4 and GATA-3 expression through TGF-β pathway [52]. In mouse models, the intravenous administration of MSCs can downregulate Th2 immunoglobulin IgG1 and IgE levels in serum, decrease Th2 cytokines (e.g., IL-4, IL-5, and IL-13) levels in bronchial lavage, and reduce mucus secretion and eosinophil infiltration in lungs [53].

Recently, many studies have focused on both the exosomes and anti-inflammatory soluble factors that are derived from MSCs. The exosomes are very small extracellular vesicles that carry lipids, microRNAs, DNA fragments and proteins to several targeted cells, including immune cells, endothelial cells, and pericytes. Notably, MSC-derived exosomes can alter the antigen-specific CD4+ Th2 and Th17 cell phenotype in the allergy-induced airways inflammation animal models [50]. Similarly, in peripheral blood asthmatic mononuclear cells, MSC-derived exosomes promote the proliferation and immunosuppressing property of Tregs, and enhance the production of anti-inflammatory cytokines (e.g., IL-10 cytokine and TGF-β) [54]. The intravenous administration of MSCs could downregulate Th2 immunoglobulin IgG1 and IgE levels in serum, decrease Th2 cytokines (e.g., IL-4, IL-5, and IL-13) levels in bronchial lavage, and reduce mucus secretion and eosinophil infiltration in lungs [53] (**Figure 1**).

Group 2 innate lymphoid cells (ILC2s) are highly activated in asthma and a major regulator of inflammation in the lung (type 2) since they can both produce IL-5, IL-13, and IL-9 cytokines, and to initiate type 2 immune response [55]. MSCs can suppress severe asthma by regulating ILC2s [47]. For example, iPSC-derived MSCs (iPSC-MSCs) can directly enhance the functions of ILC2 through interaction with ICOS-ICOSL. In contrast, iPSC-derived MSCs can inhibit ILC2s by activating Treg cells, which secret IL-10 to suppress ILC2s [56, 57]. MSC-based suppression of lung myeloid DCs was also well-investigated using asthmatic mouse models. Indeed, DCs displayed reduced abilities to present antigen, activate naive T cells and effector Th2 cells, and migrate to mediastinal lymph nodes after treatment with MSCs [58]. The modulatory effects of MSC-derived exosomes on DC-induced immune response have also been studied in mouse models. MSC-derived exosomes can suppress bone marrow derived-DCs maturation, decrease both DC surface marker expression and IL-6 release, and increase the release of IL-10 and TGF-β [59].

MSCs can reduce lung inflammation, reduce bronchial hyperresponsiveness and improve lung function through limiting the production of chemokine (C-C motif) ligands (e.g., CCL17, CCL22), which are vital for the migration of effector Th2 cells in inflamed mouse lungs [58]. As a result, the level of IL-5, IL-4 and IL-13 pro-inflammatory cytokines, and serum IgE and mucus secretion, as well as the number of lung-infiltrating eosinophil cells were reduced [58].

MSCs can mediate the attenuation bronchial asthma via MSCs-alveolar macrophage interaction [60]. Macrophage cells can clearly develop into an immunosuppressive/anti-inflammatory M2 phenotype after transplantation with MSCs, and thereby can increase the formation of important immunosuppressive factors like COX-2, which can reduce inflammation but enhance the regeneration of asthmatic lungs [60]. This was further supported by studying asthma using murine models. For example, the cross-talking between alveolar macrophage cells adipose tissue-derived MSCs (AT-MSCs) or BM-MSCs decreased pro-inflammatory properties of alveolar macrophages in mouse treated with MSCs [61]. Another study showed that, MSCs modulate macrophage polarization via activating aryl hydrocarbon receptor (AhR) signaling during asthma [62].

Besides the anti-inflammatory effect, MSC-based treatment has several other effects. For example, MSCs can prevent pulmonary airway remodeling in MSC-treated asthmatic mice by reducing resistance, viscoelastic pressure, collagen deposition, and bronchoconstriction index of the lung parenchyma [49, 51]. Furthermore, MSC-based therapy can reduce the production of reactive oxygen and nitrogen species. Intravenous administration of human BM-MSCs can reduce nitro-tyrosine levels and is important for the maintenance of oxidative homeostasis in the lung of the animal model of asthma [63]. Furthermore, MSCs can increase alveolar differentiation as well as reduce renewal ability of lung progenitor cells in 3D organoid cultures [64].

Three singling pathways: Notch, phosphoinositide 3-kinase (PI3K)/Akt and TGF-β1/Smad

have been identified as major MSC molecular targets in asthmatic lungs [65-67]. The Notch signaling pathway is an evolutionarily conserved pathway that plays essential roles in cell fate determination, cell differentiation, and tissue homeostasis. In asthma, Notch signaling has been implicated in various processes, including airway inflammation, airway remodeling, and immune cell responses [66]. The Akt/PI3K pathway is essential for cell survival, growth, and metabolism. In asthma, this pathway is involved in regulating multiple aspects of airway inflammation and hyperresponsiveness [65]. TGF-beta pathway is a multifunctional signaling pathway involved in cell growth, differentiation, and tissue repair. In asthma, TGF-beta signaling is associated with airway remodeling and immune regulation [67]. Treatments of the asthmatic lung of rat models with human MSCs can lead to a reduced expression level of Notch (Notch-1 and Notch-2) and jagged-1. However, it can also increase the expression level of other Notch (e.g., Notch-4 and Notch-3), as well as delta-like ligand (delta)-4 in those asthmatic lungs [66]. In rat asthmatic lungs, MSC administration could modulate Notch signaling to reverse goblet cell hyperplasia [66]. In addition, in asthmatic lungs of rats, transplanted MSCs can suppress PI3K signaling by inhibiting the expression Akt phosphorylation and thereby suppress airway remodeling and inflammation [65]. Together with IFN-γ, iPSC-MSCs could effectively prevent airway remodeling in chronic allergic airway inflammation, through reducing TGF-β1 production in the lung via TGF-β1-Smad2/Smad3 signaling pathway [51, 67].

Several clinical studies have tested both the safety and effectiveness of MSC-based therapies of patients with asthma. For instance, preclinical studies that involved the intra-articular administration of MSCs in dogs models showed that MSC-based therapy is safe and efficient with benefits over a 24-month period [68]. In addition, one clinical trial NCT03137199 tested the safety of allogeneic BM-MSCs in treating asthma. This trail involved the intravenous administration of BM-MSCs into two groups of asthmatic patients who received different doses (total 6 patients). Lung volume and function, peripheral eosinophilia and dyspnea and quality of life were assessed and tested every 4 weeks. The phase 1 clinical trial NCT03137199 was terminated in 2020. Interestingly, the safety and effectiveness of MSC-derived factors such as the allogeneic hUC-MSC-derived trophic factor (MTF) was also tested in 20 adult patients with asthma in NCT02192736 clinical study. The phase 1 clinical trial NCT02192736 was also completed in 2020.

MSC-based attenuation of pneumonia and ARDS

The ARDS (acute respiratory distress syndrome) is a serious injury in the lung, in which fluids accumulate in the lung due to alveolar-epithelial barrier's disruption. The progression of ARDS is usually associated with other physiological changes such as the infiltration of inflammatory cells and interstitial edema and can lead to an acute respiratory failure [69, 70]. This respiratory failure is characterized by both enhanced matrix deposition and increased proliferation of type II pneumocyte cells, fibroblast cells, and myofibroblast cells [71]. Without pharmacologic treatments, the ADRS can be life-threating with a high mortality rate (34-44%) [72]. Notably, the infection with SARS-CoV-2 virus has been a major cause of the ADRS since 2019. This infection can destroy alveolar epithelial cells and induce the secretion of proinflammatory cytokines [73].

Both MSCs and MSC-derived secretome have been used for the treatment of the ARDS in some preclinical studies. Since the infection with gram-negative bacteria usually cause the development of the ARDS [74], MSC-based therapies hold promise for preventing the development of the ARDS in animal models of bacteria-derived lipopolysaccharide (LPS)-induced sepsis [75]. Indeed, MSCs can be used to ameliorate the inflammation in the alveoli of the murine model of the ARDS that was induced by LPS in a paracrine way without a direct cell contact [76]. Mechanistically, MSCs can mediate a decrease in the expression level of inflammatory TNF-α and the inflow of neutrophil cells into the lung tissue, in an IL-10-dependent manner [76, 77]. In addition, in the ARDS-injured lungs, MSCs can promote AT2 cell regeneration and the repair of alveolar-epithelial barrier by the secretion of certain types of growth factors and other molecules such as the keratinocyte growth factor (KGF), HGF, vascular endothelial growth factor (VEGF), angiopoietin-1, interleukin 1 (IL-1) receptor antago-

nist (IL-1RN), prostaglandin E2 (PGE2), and both scavenging oxidants and radicals [75, 78-80] (**Figure 1**).

Furthermore, MSCs can reverse the epithelial-mesenchymal transition (EMT) process through inhibiting NF-κB and Hedgehog pathways [81]. MSCs can also reduce the expression of both TRL4 and Mdy88 mRNAs [82]. Moreover, MSCs can stimulate the production of anti-inflammatory IL-10 by macrophage cells, and thereby increase the protection against sepsis-associated the ARDS [48, 53]. Reversely, IL-10 can downregulate the expressions of AT2-related genes [83]. Notably, these MSC-mediated effects can improve oxygenation, reduce pulmonary edema, and increase the survival of MSC-treated animal models [75, 84]. In addition, when growing in culture with AT2 cells, human MSCs can produce certain mediator factors, including Lipoxin A4 (LXA4; a pro-resolving mediator lipoxin A4) that can attenuate pulmonary edema and improve the survival of murine animal models suffering the ARDS that is induced by the LPS [85] (**Figure 1**).

The potency of MSCs in treating the ARDS depends on certain immunomodulatory factors which can reduce the differentiation of MSCs into AT2-like cells. For instance, studies have shown that microRNA-615-3p and microRNA-155-5p can modulate the activity of immune cells and cytokine production and overexpressed microRNA-615-3p or microRNA-155-5p was able to attenuate the differentiation of MSCs into AT2 cells through Wnt/β-catenin pathway [86].

Furthermore, MSCs therapeutic potentials of MSCs were evaluated in multiple clinical trails (**Table 1**) that focused on the treatment of the ARDS by measuring biomarkers of ARDS, such as IL-6, IL-8, and SP-D [87, 88]. One of these clinical trials conducted by Fizsimmons and coworkers [2], illustrated that allogeneic bone marrow-derived MSCs (BM-MSCs), which were intravenously infused alone, can be tolerated by nine ARDS patients without dose-limiting toxicity or clinical instability, and significant reduce the lung injury [88]. However, another clinical study (NCT01902082) on twelve ARDS patients, have shown that allogeneic administration of MSCs is safe but not efficient [87]. The change of ARDS biomarkers expression examined in patients the after treatment was not significant compared to the placebo group [87].

The infusion of maximum 3 million cells/kg of MSCs have been clinically shown not to elevate the proinflammatory cytokines levels, while transiently dampening pro-inflammatory cytokines, suggesting a mechanism associated with innate immunity [89]. The safety and efficiency of MSCs transplantation in treating moderate to severe ARDS were also evaluated in Phase I and II clinical studies [90].

ARDS and pneumonia are closely related because pneumonia is the common cause of ARDS.

ARDS is mainly caused by nosocomial pneumonia [91]. When lungs become inflamed during ARDS or pneumonia, the concentration of inflammatory chemokines, including CXCL8 and CXCL1, increased that can result in attracting more CD4+ Th1 and neutrophil cells, leading to more production of inflammatory gamma-interferon (IFN-γ-). In addition, these physiological changes ultimately result in increased secretion of proteolytic enzymes and inflammatory cytokines from alveolar [92]. In addition, macrovesicles produced by MSCs can promote phagocytic activity of alveolar macrophages, enhance clearance of alveolar fluid, and lower the load of bacterial in Gram-negative E. coli-induced pneumonia [93]. Furthermore, antimicrobial proteins produced by MSCs and their inhibitory effect on bacterial growth have also been reported in flamed lungs [94]. Indeed, the lung inflammation, injury, and survival of experimental animals suffering from bacterial pneumonia were improved after administrating MSCs intratracheally [93]. The stimulation of clearance of bacteria occurred in a lipocalin-2 dependent manner [93, 94].

MSC-based treatment approaches of the IPF

One of the well-known features for the lungs is their limited capacity for regeneration, compared to other body organs. The current drugs are not efficient for pulmonary fibrosis [95, 96]. Therefore, several therapeutic agents such as Nintedanib and Pirfenidone approved by FDA, can only slow down the decline of lung function in patients with the IPF [97, 98].

The pathogenesis of IPF is associated with the imbalanced homeostasis in pulmonary epithe-

lium [98, 99]. Several studies showed that an aberrant damage of the alveolar epithelium can activate alveolar epithelial cells (AECs) to secrete coagulant, pro-fibrotic and inflammatory cytokines which activate fibroblasts to proliferate and differentiate into myofibroblasts, and thereby secrete proteins forming the extracellular matrix (ECM) [100]. Fibroblast cell proliferation, repetitive lung injury, increased AT2 cell apoptosis, enhanced extracellular matrix deposition, and abnormal epithelial-mesenchymal cell interactions have all been identified as IPF pathological changes in several clinical studies [101-107]. The epithelial-mesenchymal transition can destruct lung structures, leading to fibrosis progression and a decline of the lung [108]. However, the factors that trigger the IPF remains unknown and currently under investigation, including the environmental and genetic factors that can cause dysfunctions in AT2 cells, leading to fibrogenesis [109].

MSCs have been widely considered as potential therapeutic approaches for the IPF, because they can promote the generation of AT2 cells, reduce the secretion of degradative enzymes and suppress the production of profibrotic factor from immune cells infiltrated in the lung [110-116]. Interestingly, the administration of MSCs can lead to preventing irradiation-induced lung fibrosis, via inhibiting collagen accumulation, inflammatory cytokine production and fibroblast proliferation [110].

The most used experimental model of pulmonary fibrosis is the bleomycin-induced pulmonary fibrosis. Several studies have used this model to show that MSCs can be transplanted into bleomycin-injured lungs within a short period of time (4 hours). In addition, injected MSCs can reduce lung inflammation and edema, collagen deposition and mortality, and improve histopathology. The administration of MSCs can also lead to reduced activities of matrix metalloproteinase-9 (MMP-9), metalloproteinase-2 (MMP-2), and metalloproteinase-13 (MMP-13) [116]. Moreover, transplanted MSCs can protect against bleomycin-induced lung damage and fibrosis [113, 116], because they can reduce TGF-beta in indigenous macrophage cells and immune cells infiltrated in the lungs. They can also attenuate many inflammatory cytokines such as IL-1, TNF-, and IL-6 [112, 114]. In addition, research studies suggested that the abnormal activation of the TGF-beta and Wnt/β-catenin signaling pathways can cause lung-resident MSCs to differentiate into myofibroblasts, leading to the development of the IPF [83]. Consequently, treatment with ICG-001, an inhibitor of Wnt/β-catenin pathway, prevented MSCs from transforming to myofibroblasts and thereby protects against bleomycin-induced fibrosis in the lung. Furthermore, inhibiting TGF signaling activity under hypoxic settings can greatly reduce MSC differentiation into fibroblast-like cells generated by TGF [117]. Downregulation of Snail, a key component in EMT regulation that inhibits metastasis associated gene 1 (MTA1), can also reverse TGF-induced EMT [118] (**Figure 1**).

Several researchers have examined the significance of MSC-derived exosomes in the treatment of pulmonary fibrosis. They found that MSC-derived exosomes are able attenuate lung fibrosis, promote lung repair/regeneration, and restore lung function [111]. In addition, Exosomes d-MAPPS are specific MSC-derived exosomes containing concentrated immunomodulatory proteins and factors, which can reduce pulmonary airway inflammation but enhance pulmonary functions in chronic lung inflammation' patients in a pilot clinical trial [115]. Indeed, MSC-derived exosomes can also prevent and reverse experimental lung fibrosis via altering monocyte phenotype [119].

MSCs were used in a variety of clinical trials (**Table 1**) because of their safety and efficacy in the treatment of the lung fibrosis. For instance, a well-known clinical trial (NCT01385644) focused in its phase 1 on the therapeutic and healing potentials of mesenchymal stromal cells derived from the placenta (PL-MSCs) in the treatment of the IPF. In this study, eight patients were given intravenous injections of 1 or 2 million PL-MSCs per each kilogram (kg) of body weight. Both doses (1 or 2 million PL-MSCs) have been well-tolerated by the involved patients in the study. Injections of PL-MSCs, on the other hand had no effect on the IPF in these patients [120]. In another phase 1 clinical research (NCT02013700), nine patients with the IPF were given 20, 100, or 200 million allogeneic MSCs intravenously and observed for almost 14 months. Unfortunately, two of treated patients in this study died, because of IPF development, while five others

reported a variety of side effects [121]. In contrast, the intrabronchial injection of allogenic AT-MSCs that are derived from adipose tissues were a safe treatment that led to improving the health and life parameters in patients with the IPF [122] and did not cause severe side effects in these patients within two years of treatment with MSCs [123].

In 2021, a phase I multicenter clinical trial (NCT01919827) in patients with mild-to-moderate IPF evaluated the feasibility, efficiency and safety of autologous BM-MSCs that were administrated endo-bronchially. The findings of this clinical trial revealed that whereas endo-bronchially infused BM-MSC cells cannot induce substantial unfavorable effects in patients with the IPF immediately, a significant number of patients experienced both functional and clinical advancement. However, the genomic instabilities of BM-MSCs reported during growing in culture can be problematic for the wide application of autologous MSCs in the treatment of patients with the IPF [124]. These clinical trials indicate the origin of the MSCs whether they were autologous or allogeneic is important.

MSC-based treatment of COPD patients

The COPD (a chronic obstructive pulmonary disease) is a chronic inflammatory disease, which creates airflow blockages in the lung. COPD is defined by the deterioration of the parenchyma that leads to emphysema, and terminal bronchi that causes obstructive bronchitis in the lung, as well as limited airflow due to noxious gases or particle particles [125]. Other changes that contribute to the development of COPD include several alterations in the oxidative stress, immune cells infiltrating the lung, and the balance between active proteases and their inhibitors [126]. Smoking history, airway hyperresponsiveness, and parental history of asthma are all key risk factors for the development of COPD [127]. Tobacco smoking can also affect the immunomodulatory capacity of smokers with COPD in an in vitro investigation [128].

Due to their unique ability to suppress harmful immunological responses, preserve oxidative homeostasis, and control the enzymatic activities that degrade the matrix, MSCs have shown potential in multiple experimental and clinical investigations for the treatment of COPD [129, 130]. The infusion of adipose tissue-MSCs and BM-MSCs showed both safe and promising results for COPD treatment in experimental animal models in which COPD was induced by either elastase instillation or cigarette smoke exposure [129, 130]. Furthermore, intratracheal or intravenous MSCs can successfully migrate and transplant into the lungs within 24 hours of MSC treatment in COPD animal models [131-134]. This can result in a significant reduction in alveolar damage, alveolar cell loss, and other emphysema-related alterations [135, 136]. In addition, MSC-treated animal models of COPD showed a significant improvement in the lung function, forced expiratory volume, dynamic compliance, and mean forced expiratory flow [130]. MSC-based treatments can also lead to a reduction in the number of inflammatory cells in the peri-bronchial, alveolar septum and peri-vascular interstitium [135, 137].

Through the anti-inflammatory and other mitochondrial transfer pathways, MSCs plus MSC-derived exosomes combination treatment or combined antioxidant, anti-inflammation, and MSC treatment may reverse mitochondrial dysfunction caused by a cigarette smoke exposure [138, 139]. Notably, human Wharton's jelly derived MSCs showed certain lung regeneration benefits in COPD animal models [140]. In rat models of COPD, the transplantation of hUC-MSC (human umbilical cord mesenchymal stromal cell) and administration of extracellular vesicles can effectively reduce COPD-induced airway inflammation [12, 141] (**Figure 1**).

In COPD animal models, transplanted MSCs can primarily target macrophages. Mechanistically, MSCs can reduce the production of PGE2 and expression of cyclooxygenase-2 (COX2) in alveolar macrophages by producing certain growth factors and cytokines such as HGF, IL-10 and TGF-β [134]. Remarkably, MSCs can block the production of PGE2 and COX2 in inflammatory M1 macrophages through the MAPK-ERK signaling pathway, causing these cells to become polarized towards an anti-inflammatory M2 macrophage's phenotype [134, 142]. After MSC administration, high levels of anti-inflammatory cytokines and growth factors, including IL-10 and TGF that are derived from M2 macrophage cells were detected in animal models of COPD. These MSCs can significantly improve the lung structure by reduc-

ing the secretion of elastic fibril-degrading metalloproteinases, including MMP-2, MMP-9, and MMP-12 [130, 134, 135, 142]. The inhibition of apoptosis in alveolar cells in COPD animal models treated with MSCs is another mechanism. Indeed, COPD murine models that were treated with MSCs had lower levels of pro-apoptotic Bax and higher levels of anti-apoptotic Bcl-2 gene expression, which resulted in less apoptosis in alveolar type II epithelial cells [143]. Similarly, reduced apoptosis in alveolar type II epithelial cells was linked to caspase 3, a major modulator of MSC-dependent apoptosis regulation [144] (**Figure 1**).

The second therapeutic role of MSC in COPD is to differentiate into structural lung cell types [143, 145, 146]. By stimulating the canonical Wnt/beta-catenin signaling pathway in vitro, transplanted MSCs engrafted into lung tissues can develop into functional alveolar type II epithelial-like cells expressing SPC [143, 145]. Transplanted MSCs have been shown to protect against emphysema [143]. Furthermore, transplanted MSCs can increase the cell proliferation of epithelial progenitors, which will replace the diseased or injured alveolar type II epithelial cells, resulting in enhanced lung function in COPD animal models treated with MSCs [145]. However, more research studies are needed to determine the signaling molecules and pathways that control MSC differentiation into alveolar type II epithelial-like cells in vivo.

The allogeneic human MSCs treatment of 62 patients with COPD can inhibit inflammation since these patients showed reduced levels of serum C-reactive protein [95]. However, these treatments did not significantly alter the lung function or the indicators of quality of life compared to untreated patients with COPD [95]. Notably, a systemic administration of hUC-MSC can lead to improving the life quality of COPD patients in another clinical study (ISRCTN704-43938) [147]. Furthermore, a recent study by Hoang and co-workers [148] has established a matched case-control trial of allogeneic hUC-MSCs (phase I/II) for COPD patients.

MSC transplantation and its therapeutic effect in the lung

MSC-treated IPF patients showed a decline in their lung functions almost 2 years after MSC administration for the first time, suggesting that more efficient therapies and treatment strategies are needed for prolonging the effect of MSC therapy [123]. Several other studies have developed strategies to improve the engraftment and survival of MSCs in the injured lungs, since effective engraftment, homing, and viability are essential for enhancing MSC therapeutic efficacy in the lung after injury [57]. The overall goal of these strategies was to optimize the culture conditions of MSCs, overexpress growth factors in MSCs or induce autophagy in MSCs [149-154]. For example, hypoxia-induced autophagy of MSCs can increase the survival of MSCs in the lungs [154]. In addition, overexpression of HIF-1α in MSCs can remarkably enhance the efficiency of MSC-based therapy for pneumonia [153]. Notably, efficient cryopreservation and freeze-thawing processes are important for MSC-based treatment safety and efficacy. These two processes are critical for MSC product safety and for enhancing MSC applications in clinical trials (**Table 1**). Optimizing these two processes and related manufacturing process designs can, therefore, enhance both the efficacy and safety of MSC-based therapy in clinical use. More research is still needed on this topic.

Treatments with other factors can also improve the survival and therapeutic efficiency of MSCs. For example, MSCs pretreated with the pleiotropic cytokine, Oncostatin M (OM), can survive and significantly improve lung functions in the bleomycin-induced lung fibrosis in mice [152]. Furthermore, a recently generated MSC-derived immunity-and-matrix-regulatory cells can remarkably reduce both lung fibrosis and inflammation in a murine model of lung injury [155].

Most recent progress in the application of mesenchymal stromal cell-based therapy in lung diseases

In the last three years, there is a rapid progress in the use of MSCs in lung diseases and research. In addition, more attention has been paid to the application of exosomes and extracellular vesicles in respiratory disorders and diseases [156-159]. For example, exosomal miR-7704 from MSCs was used for modulating experimental acute lung injury. This finding can help with better understanding the therapeutic potentials of exosomal miRNAs in inflamma-

tory diseases of the lung [160]. In addition, exosomes from adipose-derived MSCs that are loaded with Nintedanib drug and tyrosine kinase inhibitor can inhibit pulmonary fibrosis that is induced by bleomycin in the animal model of fibrosis [161]. Similarly, adipose tissue-derived MSCs can attenuate both pulmonary fibrosis and inflammation in the bleomycin-induced lung fibrosis animal model via caveolin-1/NF-κB signaling axis [162]. In addition, the potential use of both MSCs and their exosomes in the treatment of neural disease such as Parkinson disease is well reported [163]. Similarly, extracellular vesicles from umbilical cord MSCs can protect against fibrosis and oxidative stress in an experimental animal model of bronchopulmonary dysplasia [164]; while olfactory mucosa derived MSCs can alleviate pulmonary fibrosis through the reduction of inflammation [165]. Remarkably, MSC-based therapy is promising in the alleviation of both aging [166], and acute respiratory distress syndrome through the cholinergic anti-inflammatory pathway [167]. Moreover, MSC-derived extracellular vesicles can reprogram macrophage cells in ARDS disease models [168] and have potential benefits in regulating the inflammatory responses after COVID-19-induced ischemic events [169], in treating both acute lung injury and acute respiratory distress syndrome [170, 171], and in the treatment of COVID-19 disease [159].

Notably, MSC can also affect lung injury that is associated with other diseases. For instance, MSCs can activate Nrf2 antioxidation pathway, resulting in the inhibition of ferroptosis in severe acute pancreatitis-associated acute lung injury [172]. Interestingly, MSCs can also inhibit ferroptosis and block the formation of neutrophil extracellular traps, leading to the alleviation of sepsis-induced acute lung injury in rats [173]. In addition, MSCs can suppress both lung and skin inflammation and fibrosis in topoisomerase I-induced systemic sclerosis that is associated with lung disease murine model [174]. Moreover, MSCs can attenuate the pattern of proinflammatory cytokines in the animal model of chronic cigarette smoke exposure [175]. Furthermore, MSC-based therapy can modulate both the expression of miR-193b-5p, leading to the attenuation of sepsis-induced acute lung injury [176], and the polarization of lung macrophages and exerts anti-asthmatic effects [177]. Moreover, there is an increase interest toward using MSCs in innovative gene vectors or drugs for cancer treatments [178].

Most recent clinical trials (**Table 1**) have evaluated the efficiency and safety profile of adipose-derived MSCs for treating severe community-acquired bacterial pneumonia. The found that these stem cells were well tolerated in this severe pneumonia [179]. Similarly, the therapeutic option of MSCs in other respiratory disease patients such as COPD, ARDS and COVID-19 patients is well reported [180-183]. Interestingly, a recent phase I study assessed the tolerability and safety of allogeneic MSC infusion in cystic fibrosis patients and found that the allogeneic MSC intravenous infusions is well-tolerated and safe [184]. In addition, Wharton jelly derived MSCs is a potential therapy for patients with lung fibrosis [185]. Notably, treatment of newborns with MSCs or MSC-derived extracellular vesicles may lead to improving lung architecture, decreasing lung inflammation, attenuating lung fibrosis, enhancing the survival rate, and treating bronchopulmonary dysplasia [186].

Final conclusions and future directions

MSCs are required for the cell-based therapy of diseases and/or injured lung due to their immunomodulatory and regenerative properties as well as their limited side effects in experimental animal models. Immune cells have key roles in the pathogenesis of multiple lung diseases. MSCs have a remarkable effect on these immune cells by modulating their activity, proliferation, and functions. MSCs can inhibit both the infiltrated immune cells and detrimental immune responses in the lung.

MSCs are also an important source for AT2 cells. These MSC-derived functional AT2-like cells can be used to treat serious pulmonary disorders and diseases such the ARDS, asthma, COPD, acute lung injury, and IPF in experimental animal models. Interestingly, recent studies showed that MSCs can be used for treating lung diseases that are caused by a virus infection such as Tuberculosis and SARS-COV-2 [187].

Furthermore, the extracellular vesicles that are derived from MSCs can be employed in regenerative medicine. Interestingly, MSC-derived

exosomes showed anti-inflammatory, anti-apoptosis, immunomodulation, and neovascularization effects [188], while MCS-EVs can stabilize the mitochondrial damage by attenuating both mitochondrial inflammation and damage [189]. More research studies are still needed to determine the underlying molecular and cellular mechanisms of these effects.

More studies and clinical trials are required to determine the optimum number of MSCs for transplantation and control the differentiation of MSCs into undesired cell types after transplantation. The results of these studies are required to widely apply MSC-based therapy in clinical settings for lung diseases. In addition, future research should focus on the identification and characterization of regulatory signaling pathways of MSC behavior (i.e., proliferation, differentiation, or death) and MSC fate after administration in vivo.

In conclusion, there are a continues progress and rapid pace in the stem cell-based therapeutic approaches of pulmonary diseases, including IPF, asthma, COPD, and other diseases. Indeed, there are accumulated data and findings from preclinical studies that suggest the therapeutic potential of MSCs in these diseases. Several early clinical trials suggest the safety of MSC administration, with few reported adverse effects in these trials. However, there are certain substantial challenges that should be overcome before using MSCs in clinical practice. Importantly, developing a rational approach for MSC-based clinical trials requires more research to better understand MSC mechanisms of action in the treatment of lung diseases. This research will have high impact on MSC applications since, to date, very little is known about the fate of transplanted MSCs, and few clinical trials have shown clinical improvements of patients for longer periods than 12 months. More research studies are also still needed on transplanted MSC biodistribution after longer periods to further explain MSC long-term clinical impacts.

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Disclosure of conflict of interest

None.

Abbreviations

ARDS, acute respiratory distress syndrome; AT2, alveolar type II epithelial cell; BM-MSC, Bone marrow-derived mesenchymal stromal cell; COPD, chronic obstructive pulmonary disease; DCs, dendritic cells; HGF, hepatocyte growth factor; hUC-MSC, human umbilical cord mesenchymal stromal cell; IDO, indoleamine 2,3-dioxygenase; IL-2, interleukin 2; IL-10, interleukin 10; IPF, idiopathic pulmonary fibrosis; iPSC-MSC, mesenchymal stromal cells derived from induced pluripotent stromal cell; MSC, mesenchymal stromal cell; NO, nitric oxide; OM, oncostatin M; PGE2, prostaglandin E2; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

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