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Mesenchymal stem cell-derived exosomes for the treatment of pulmonary diseases

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Abstract

Emission of air pollutants, long-term tobacco use and advanced age can cause a variety of pulmonary diseases, which are associated with high mortality rates and pose a serious threat to human health. Recent studies have found that mesenchymal stem cells (MSCs) can independently migrate to the injured site, repair damaged tissues and participate in the regulation of systemic inflammation and immune response. These properties make the use of MSCs a promising therapeutic approach for the treatment of pulmonary disease, resulting in remarkable future clinical prospects. Exosomes are a type of extracellular vesicles which can participate in various physiological activities by regulating intercellular communication. Exosomes released into the extracellular space can also affect the host immune system. MSC-derived exosomes carry bioactive molecules such as proteins, lipids, mRNAs and microRNAs, which have higher safety profile and therapeutic potential compared to cell-based therapies. In this review, we summarize and discuss the preclinical and clinical studies conducted in recent years and the mechanisms of action of MSC-derived exosomes in the treatment of pulmonary diseases.

Introduction

Emission of air pollutants, long-term tobacco use, and advanced age can cause a series of pulmonary diseases, which are associated with high mortality rates and pose a serious threat to human health. Pulmonary diseases can result from the involvement of the lung parenchyma, respiratory airways, and/or blood vessels. Accumulating evidence from preclinical and clinical studies indicates that mesenchymal stem cells (MSCs) play a crucial role in the repair of lung injury in several pulmonary diseases (such as acute lung injury and respiratory distress syndrome) by virtue of their ability to secrete paracrine agents that exert anti-inflammatory and immunomodulatory effects[1-4]. In addition, MSCs can improve lung damage through their ability to differentiate into pulmonary epithelial and endothelial cells[3]. Exosomes are a type of extracellular vesicles containing a lipid bilayer membrane, which participate in the transmission of information between cells. In recent years, many studies have shown that exosomes carry a variety of bioactive molecules and act as the main media for the function of MSCs [5]. MSC-derived exosomes (MSCs-Ex) have biological functions similar to those of MSCs, even though they are potentially superior to MSCs in terms of clinical applications and storage. The potential therapeutic value of MSCs-Ex has been widely discussed and investigated by researchers during the last years.

Mesenchymal stem cells (MSCs)

MSCs are non-hematopoietic multipotent stem cells with high capacity of self-renewal, expansion and differentiation potential, which originate from the embryonic mesoderm[6]. MSCs secrete a complex set of bioactive molecules and exhibit immunomodulatory, anti-inflammatory and antimicrobial properties; these cells have shown promising results for repairing damaged tissues in several degenerative diseases (including pulmonary diseases), both in animal and human studies[7, 8]. In a rat model of ischemia/reperfusion lung injury, hy-

poxia-preconditioned rat MSCs have been shown to reduce the degree of ischemia/reperfusion lung injury through anti-inflammatory, anti-oxidant and anti-apoptotic actions[9]. In a study conducted on a novel bleomycin-induced pulmonary fibrosis model established in humanized mice, human MSCs were able to attenuate pulmonary fibrosis and improve lung function by inhibiting bleomycin-induced T cell infiltration and production of pro-inflammatory cytokines in the lungs[10]. This study also showed that the MSC-induced alleviation of pulmonary fibrosis was mediated by the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 pathway, suggesting this pathway as a potential novel target for the treatment of pulmonary fibrosis[10].

MSC-derived exosomes (MSCs-Ex)

Exosomes are extracellular vesicles secreted from different cell types, with a size ranging from 40 to 100 nm[11,12]. Exosomes can affect cell function and behavior by paracrine or autocrine actions; exosomes mediate signal transduction mainly through their direct contact with the cell membrane. MSC-derived exosomes (MSCs-Ex) contain a variety of bioactive molecules, such as proteins, cytokines, mRNA and non-coding RNAs, which can be delivered from cell to cell to regulate the biological function and behavior of distant target cells and tissues. Interestingly, MSCs-Ex can also downregulate inflammatory pathways, thus mediating the anti-inflammatory properties of MSCs[13-16]. Exosomes are being increasingly regarded as biomarkers and prognostic factors for several diseases, including pulmonary diseases[17-19]. As reported by Levänen et al[20], exosomes isolated from the bronchoalveolar lavage fluid of asthmatic patients contain a specific exosomal microRNA (miRNA) profile, which is significantly different from that observed in the control group and can be regarded as an early biomarker for diagnosis of asthma. Several exosome surface proteins are transmembrane proteins, such as CD9, CD81 and CD63, and can be used for detection and isolation of circulating exosomes; also, changes in the expression of such proteins can also indicate the emergence of some diseases[21].

Clinical applications of MSCs-Ex in pulmonary diseases

Acute lung injury (ALI)

Acute lung injury (ALI) is a disorder of acute inflammation that leads to the disruption of the alveolar-capillary barrier, resulting in the accumulation of protein-rich alveolar fluid and inflammatory cells in the alveolar space. ALI can be caused by a number of insults, such as sepsis, pneumonia, trauma and drug toxicity. Inflammation plays an important role in the pathogenesis of many pulmonary diseases. MSCs-Ex can reduce ALI in mice by regulating inflammatory responses[22]. MiR-21-5p is an anti-apoptotic miRNA carried by MSCs-Ex that can reverse oxidative stress-induced cell death. It has been shown that intratracheal administration of MSCs-Ex or miR-21-5p agomir can inhibit M1 polarization of alveolar macrophages, decrease alveolar macrophage secretion of high mobility group box 1 (HMGB1) protein, interleukin (IL)- 8, IL-1β, IL-6, IL-17 and tumor necrosis factor-alpha (TNF-a), and significantly reduce lung injury caused by pulmonary edema and ischemia/reperfusion[23]. At the same time, in a mouse model of ALI Moon et al[24] also confirmed that exosomes derived from pulmonary epithelial cells can activate macrophages to reduce pulmonary injury. However, exosomes can also induce inflammation and aggravate the development of the disease. Indeed, Yuan et al[25] used the mouse model of acute septic lung injury induced by lipopolysaccharide to investigate the role of exosomes in the inflammatory response. This study indicated that bronchoalveolar lavage fluid exosomes from mice that were treated with lipopolysaccharide showed higher expression levels of miR-155 and miR-146a, which could induce the expression of pro-inflammatory cytokines. Therefore, targeting the abovementioned miRNAs may represent a novel tool for the treatment of ALI.

Activation and inhibition of multiple signaling pathways are involved in ALI pathophysiology. Targeted regulation of signaling pathways in ALI may provide a novel therapeutic approach for the treatment of ALI and respiratory distress syndrome. Studies have shown that serum amyloid A3 (SAA3) is highly expressed in ALI and confirmed that SAA3 is the target gene of miR-30b-3p[26]. In an ALI mouse model, overexpression of miR-30b-3p in MSCs-Ex has been shown to confer protective effects on type II alveolar epithelial cells, thus alleviating the disease[26]. Alveolar progenitor type II cell-derived exosome miR-371b-5p appears to serve as a niche signaling to augment alveolar progenitor type II cell survival/proliferation and promote the re-epithelialization of injured alveoli[27]. At the molecular level, exosome miR-371b-5p can orchestrate PI3K/Akt signaling by using PTEN as a direct target, thus promoting the survival and proliferation of alveolar progenitor type II cells[27].

Pulmonary arterial hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a type of pulmonary hypertension that primarily affects the pulmonary vasculature. In PAH, endothelial dysfunction and vascular remodeling progressively obstruct small pulmonary arteries[28]. PAH is defined as a resting mean pulmonary artery pressure ≥ 25 mmHg. This disease can lead to severe hypoxia, increased pulmonary vascular resistance and pulmonary pressures, increased right ventricular afterload, right heart failure, and eventually death. Causes of PAH include pulmonary vascular disease, left heart disease, lung disease or hypoxia, chronic thromboembolic disease, and a variety of other disorders such as sarcoidosis and hemolytic anemias[29]. Pulmonary inflammatory responses induced by hypoxia consist of augmented macrophage activation and increase in pro-inflammatory mediators. Intravenous delivery of mesenchymal stromal cell-derived exosomes (MEX) has been shown to inhibit vascular remodeling and hypoxic pulmonary hypertension in a murine model of hypoxic pulmonary hypertension, thus providing novel insights into the clinical applicability of exosome-based strategies for the treatment of PAH[30]. In particular, MEX were able to suppress the hypoxic activation of the transcription factor signal transducer and activator of transcription 3 (STAT3), as well as the upregulation of the miR-17 superfamily of miRNA clusters; while they increased pulmonary levels of miR-204, a miRNA enriched in distal pulmonary arterioles which is commonly downregulated in human PAH and experimental models of the diseas [30]. On the other hand, another study showed a novel mechanism of exosomes-regulated PAH, which potentially offers a new therapeutic tool for the treatment of this disease[31]. This study showed that the expression of 15-lipoxygenase-2 is upregulated in exosomes secreted from pulmonary artery endothelial cells (PAECs) under hypoxia, resulting in the subsequent activation of STAT3 signaling pathway and a marked increase in PAECs proliferation and migration[31].

Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a poorly reversible lung disease and represents one of the major causes of morbidity and mortality on a global scale[32]. COPD is characterized by persistent limitation of expiratory airflow, defects in tissue repair, chronic inflammation of the airways and abnormal lung inflammatory response to toxic particles or gases (e.g., cigarette smoke)[33]. Several factors may be involved in the occurrence, progression and exacerbation of COPD, such as chronic inflammation, air pollution, and different types of viruses[34]. Mi-RNAs carried by exosomes are also considered to be involved in the pathogenesis of COPD[35]. In fact, a typical feature of lung tissue remodeling in patients with COPD is the activation of bronchial myofibroblasts and smooth muscle hypertrophy and hyperplasia[36]. Exposure of bronchial epithelial cells to cigarette smoke can disrupt the bronchial epithelial barrier and the balance between epithelial cells and fibroblasts, thus inducing changes in exosome composition and airway remodeling. In COPD, hypoxia inducible factor-1α (HIF-1α) promotes the differentiation of airway fibroblasts into myofibroblasts by regulating the expression of fibrogenic gene α-SMA to HIF-1α response elements in the promoter. Importantly, exosomes may downregulate transforming growth factor-β (TGF-β) signaling pathway[37] (which is involved in fibroblast differentiation) and alleviate COPD[38].

Asthma

Asthma is a chronic inflammatory disorder of the airways characterized by the involvement of a variety of cells, especially mast cells, eosinophils and T lymphocytes. Airway hyperresponsiveness, defined as augmented sensitivity and reactivity of the airways to several types of stimuli, is one of the hallmarks of asthma and correlates with the disease severity. Du et al[39] revealed that MSCs-Ex upregulate IL-10 and TGF-β1 from peripheral blood mononuclear cells, thus promoting the proliferation and immunosuppressive ability of regulatory T cells. In addition, antigen presenting cell-dependent pathway has proven to be a possible mechanism involved in the MSCs-Ex-mediated regulation, thus elucidating the key role of exosomes in the immune regulation of MSCs and suggesting a therapeutic potential of MSCs-Ex in asthma.

Bronchopulmonary dysplasia (BPD)

Bronchopulmonary dysplasia (BPD) is a chronic lung disease which mostly occurs in premature infants who required oxygen therapy and mechanical ventilation for acute respiratory distress. BPD causes persistent respiratory distress and hypoxia, which can be accompanied by brain injury, PAH and other concomitant symptoms[40,41]. Hyperox-

ia-exposed BPD mice showed pulmonary inflammation with alveolar-capillary leakage, increased chord length and alveolar simplification, which was improved by treatment with MSCs-Ex[42]. In a neonatal murine model of BPD exposed to hyperoxia, treatment with purified exosomes derived from human umbilical cord or human bone marrow MSCs significantly improved lung morphology and pulmonary development, increased the macrophage phenotypic switch towards the anti-inflammatory M2 phenotype, reduced pulmonary fibrosis, and improved pulmonary vascular remodeling[43].

Conclusions

Pulmonary diseases pose a serious threat to human health. Most of the available treatments cannot achieve the desired effect at present. Therefore, several researchers focused on the potential therapeutic role of MSCs-Ex in pulmonary diseases, such as ALI, BPD, COPD, PAH and asthma. However, there are still many aspects that need to be clarified, such as the purity and yield of exosome extraction, the unclear mechanisms of action of MSCs-Ex, and whether the bioactive molecules carried by MSCs-Ex (e.g., proteins, lipids, mRNAs and miRNAs) can cause harm rather than benefit in different pulmonary diseases. Despite these limitations, MSCs-Ex warrant further investigation due to their potential therapeutic value and the promising prospects for their application in the treatment of pulmonary diseases.

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Conflict of Interest:

The authors have no conflict of interests to declare.

References

1. Feng Y, Wang L, Ma X, Yang X, Don O, Chen X, Qu J, Song Y. Effect of hCMSCs and liraglutide combination in ALI through cAMP/PKAc/beta-catenin signaling pathway. Stem Cell Res Ther 2020; 11: 2.
2. Wang XY. MSCs transplantation may be a potential therapeutic strategy for COVID-19 treatment. Eur Rev Med Pharmacol Sci 2020; 24: 4537-4538.
3. Sadeghian Chaleshtori S, Mokhber Dezfouli MR, Jabbari Fakhr M. Mesenchymal stem/stromal cells: the therapeutic effects in animal models of acute pulmonary diseases. Respir Res 2020; 21: 110.
4. Lanzoni G, Linetsky E, Correa D, Alvarez RA, Marttos A, Hirani K, Messinger Cayetano S, Castro JG, Paidas MJ, Efantis Potter J, Xu X, Glassberg M, Tan J, Patel AN, Goldstein G, Kenyon NS, Baidal D, Alejandro R, Vianna R, Ruiz P, Caplan AI, Ricordi C. Umbilical cord-derived mesenchymal stem cells for COVID-19 patients with acute respiratory distress syndrome (ARDS). CellR4 2020; 8: e2839.
5. Vyas N, Dhawan J. Exosomes: mobile platforms for targeted and synergistic signaling across cell boundaries. Cell Mol Life Sci 2017; 74: 1567-1576.
6. Naji A, Eitoku M, Favier B, Deschaseaux F, Rouas-Freiss N, Suganuma N. Biological functions of mesenchymal stem cells and clinical implications. Cell Mol Life Sci 2019; 76: 3323-3348.
7. Phinney DG, Pittenger MF. Concise Review: MSC-Derived Exosomes for Cell-Free Therapy. Stem Cells 2017; 35: 851-858.
8. Fu X, Liu G, Halim A, Ju Y, Luo Q, Song AG. Mesenchymal Stem Cell Migration and Tissue Repair. Cells 2019; 8: 784.
9. Liu YY, Chiang CH, Hung SC, Chian CF, Tsai CL, Chen WC, Zhang H. Hypoxia-preconditioned mesenchymal stem cells ameliorate ischemia/reperfusion-induced lung injury. PLoS One 2017; 12: e0187637.
10. Ni K, Liu M, Zheng J, Wen L, Chen Q, Xiang Z, Lam KT, Liu Y, Chan GC, Lau YL, Tu W. PD-1/PD-L1 Pathway Mediates the Alleviation of Pulmonary Fibrosis by Human Mesenchymal Stem Cells in Humanized Mice. Am J Respir Cell Mol Biol 2018; 58: 684-695.
11. Colombo M, Moita C, van Niel G, Kowal J, Vigneron J, Benaroch P, Manel N, Moita LF, Thery C, Raposo G. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. J Cell Sci 2013; 126: 5553-5565.
12. García-Contreras M, Messaggio F, Jimenez O, Mendez A. Differences in exosome content of human adipose tissue processed by non-enzymatic and enzymatic methods. CellR4 2015; 3: e1423.
13. Chen J, Hu C, Pan P. Extracellular vesicle MicroRNA transfer in lung diseases. Front Physiol 2017; 8: 1028.
14. Xian P, Hei Y, Wang R, Wang T, Yang J, Li J, Di Z, Liu Z, Baskys A, Liu W, Wu S, Long Q. Mesenchymal stem cell-derived exosomes as a nanotherapeutic agent for amelioration of inflammation-induced astrocyte alterations in mice. Theranostics 2019; 9: 5956-5975.
15. Garcia-Contreras M, Robbins PD. Exosomes and microvesicles: Applications for Translational Research from Biomarkers to Therapeutic Applications-2013 ASMEV Meeting Report. CellR4 2013; 1: e412.
16. Garcia-Contreras M, Ricordi C, Robbins PD, Oltra E. Exosomes in the pathogenesis, diagnosis and treatment of pancreatic diseases. CellR4 2014; 2: e807.
17. Chen F, Huang C, Wu Q, Jiang L, Chen S, Chen L. Circular RNAs expression profiles in plasma exosomes from early-stage lung adenocarcinoma and the potential biomarkers. J Cell Biochem 2020; 121: 2525-2533.
18. Xiao Y, Zhong J, Zhong B, Huang J, Jiang L, Jiang Y, Yuan J, Sun J, Dai L, Yang C, Li Z, Wang J, Zhong T. Exosomes as potential sources of biomarkers in colorectal cancer. Cancer Lett 2020; 476: 13-22.

19. Sinha N, Kumar V, Puri V, Nada R, Rastogi A, Jha V, Puri S. Urinary exosomes: potential biomarkers for diabetic nephropathy. Nephrology (Carlton) 2020 Apr 22. doi: 10.1111/nep.13720. Epub ahead of print.
20. Levanen B, Bhakta NR, Torregrosa Paredes P, Barbeau R, Hiltbrunner S, Pollack JL, Skold CM, Svartengren M, Grunewald J, Gabrielsson S, Eklund A, Larsson BM, Woodruff PG, Erle DJ, Wheelock AM. Altered microRNA profiles in bronchoalveolar lavage fluid exosomes in asthmatic patients. J Allergy Clin Immunol 2013; 131: 894-903.
21. Yu B, Zhang X, Li X. Exosomes derived from mesenchymal stem cells. Int J Mol Sci 2014; 15: 4142-4157.
22. Zhu YG, Feng XM, Abbott J, Fang XH, Hao Q, Monsel A, Qu JM, Matthay MA, Lee JW. Human mesenchymal stem cell microvesicles for treatment of Escherichia coli endotoxin-induced acute lung injury in mice. Stem Cells 2014; 32: 116-125.
23. Li JW, Wei L, Han Z, Chen Z. Mesenchymal stromal cells-derived exosomes alleviate ischemia/reperfusion injury in mouse lung by transporting anti-apoptotic miR-21-5p. Eur J Pharmacol 2019; 852: 68-76.
24. Moon HG, Cao Y, Yang J, Lee JH, Choi HS, Jin Y. Lung epithelial cell-derived extracellular vesicles activate macrophage-mediated inflammatory responses via ROCK1 pathway. Cell Death Dis 2015; 6: e2016.
25. Yuan Z, Bedi B, Sadikot RT. Bronchoalveolar Lavage Exosomes in Lipopolysaccharide-induced Septic Lung Injury. J Vis Exp 2018; 135: 57737.
26. Yi X, Wei X, Lv H, An Y, Li L, Lu P, Yang Y, Zhang Q, Yi H, Chen G. Exosomes derived from microRNA-30b-3p-overexpressing mesenchymal stem cells protect against lipopolysaccharide-induced acute lung injury by inhibiting SAA3. Exp Cell Res 2019; 383: 111454.
27. Quan Y, Wang Z, Gong L, Peng X, Richard MA, Zhang J, Fornage M, Alcorn JL, Wang D. Exosome miR-371b-5p promotes proliferation of lung alveolar progenitor type II cells by using PTEN to orchestrate the PI3K/Akt signaling. Stem Cell Res Ther 2017; 8: 138.
28. Lai YC, Potoka KC, Champion HC, Mora AL, Gladwin MT. Pulmonary arterial hypertension: the clinical syndrome. Circ Res 2014; 115: 115-130.
29. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ 2018; 360: j5492.
30. Lee C, Mitsialis SA, Aslam M, Vitali SH, Vergadi E, Konstantinou G, Sdrimas K, Fernandez-Gonzalez A, Kourembanas S. Exosomes mediate the cytoprotective action of mesenchymal stromal cells on hypoxia-induced pulmonary hypertension. Circulation 2012; 126: 2601-2611.
31. Zhang M, Xin W, Ma C, Zhang H, Mao M, Liu Y, Zheng X, Zhang L, Yu X, Li H, Zhu D. Exosomal 15-LO2 mediates hypoxia-induced pulmonary artery hypertension in vivo and in vitro. Cell Death Dis 2018; 9: 1022.
32. Devine JF. Chronic obstructive pulmonary disease: an overview. Am Health Drug Benefits 2008; 1: 34-42.
33. Angelis N, Porpodis K, Zarogoulidis P, Spyratos D, Kioumis I, Papaiwannou A, Pitsiou, G, Tsakiridis K, Mpakas A, Arikas S, Tsiouda T, Katsikogiannis N, Kougioumtzi I, Machairiotis N, Argyriou M, Kessisis G, Zarogoulidis K. Airway inflammation in chronic obstructive pulmonary disease. J Thorac Dis 2014; 6 (Suppl 1): S167-S172.
34. Lee J, Jung HM, Kim SK, Yoo KH, Jung KS, Lee SH, Rhee CK. Factors associated with chronic obstructive pulmonary disease exacerbation, based on big data analysis. Sci Rep 2019; 9: 6679.
35. Salimian J, Mirzaei H, Moridikia A, Harchegani AB, Sahebkar A, Salehi H. Chronic obstructive pulmonary disease: MicroRNAs and exosomes as new diagnostic and therapeutic biomarkers. J Res Med Sci 2018; 23: 27.
36. Salazar LM, Herrera AM. Fibrotic response of tissue remodeling in COPD. Lung 2011; 189: 101-109.
37. Yao Y, Chen R, Wang G, Zhang Y, Liu F. Exosomes derived from mesenchymal stem cells reverse EMT via TGF-β1/Smad pathway and promote repair of damaged endometrium. Stem Cell Res Ther 2019; 10: 225.
38. Xu H, Ling M, Xue J, Dai X, Sun Q, Chen C, Liu Y, Zhou L, Liu J, Luo F, Bian Q, Liu Q. Exosomal microRNA-21 derived from bronchial epithelial cells is involved in aberrant epithelium-fibroblast cross-talk in COPD induced by cigarette smoking. Theranostics 2018; 8: 5419-5433.
39. Du YM, Zhuansun YX, Chen R, Lin L, Lin Y, Li JG. Mesenchymal stem cell exosomes promote immunosuppression of regulatory T cells in asthma. Exp Cell Res 2018; 363: 114-120.
40. Davidson LM, Berkelhamer SK. Bronchopulmonary dysplasia: chronic lung disease of infancy and long-term pulmonary outcomes. J Clin Med 2017; 6: 4.
41. Berkelhamer SK, Mestan KK, Steinhorn RH. Pulmonary hypertension in bronchopulmonary dysplasia. Semin Perinatol 2013; 37: 124-131.
42. Chaubey S, Thueson S, Ponnalagu D, Alam MA, Gheorghe CP, Aghai Z, Singh H, Bhandari V. Early gestational mesenchymal stem cell secretome attenuates experimental bronchopulmonary dysplasia in part via exosome-associated factor TSG-6. Stem Cell Res Ther 2018; 9: 173.
43. Willis GR, Fernandez-Gonzalez A, Anastas J, Vitali SH, Liu X, Ericsson M, Kwong A, Mitsialis SA, Kourembanas S. Mesenchymal stromal cell exosomes ameliorate experimental bronchopulmonary dysplasia and restore lung function through macrophage immunomodulation. Am J Respir Crit Care Med 2018; 197: 104-116.