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The Mechanism of MSCs Therapy in Acute Respiratory Distress Syndrome

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Abstract

In past decades, acute respiratory distress syndrome (ARDS) has been associated with high mortality and morbidity. Although many maneuvers have been tested including tens of clinical trials, so far there is still no approved pharmacological intervention available for ARDS except protective ventilation strategy. Mesenchymal stem cells (MSCs) has shown improved survival in various ARDS animal model after administration. Here we summarized the updates of MSC derivation and purification, administration approaches, timing of MSC delivery, and mechanism of MSC therapy in order to provide a state-of-art paradigm of cell based therapy in ARDS and to facilitate the development of MSC therapy in ARDS patients.

Keywords: Mesenchymal stem cells; Acute respiratory distress syndrome; Acute lung injury; Mechanism

Introduction

The acute respiratory distress syndrome (ARDS) is a major challenge in pulmonary and critical care medicine with high morbidity and mortality [1-3]. According to a recent multi-center study on mortality from USA in 2010, the crude mortality of ICU patients declined from 31% in 1998 to 28% in 2010 [4]. However, these epidemiological surveys of incidence and mortality lacked participations of small units of the institution and ignored medical treatment units of other degrees. Also, US Centers of Disease Control announced that, ARDS, together with COPD and IPF, represented the third fatal disease following heart diseases and cancer, which has impact on 600 million people worldwide [5]. In the ICU, ARDS is responsible for up to 40% mortality of single organ injury without MODS [6].

The pathogenesis of ARDS include: out of controlled innate immune mediated inflammatory reaction in the lungs; a variety of inflammatory response promoted aggregation and activation of a large number of inflammatory factors, which stimulated the coagulation/fibrinolysis pathway; increased alveolar epithelial and endothelial permeability; protein accumulation and formation of pulmonary edema in distal air space [7]. Thus, development of novel therapeutic strategy against ARDS need to be based on those pathophysiological changes: reduction of inflammatory factors, absorption of alveolar fluid, repair of endothelial and epithelial barrier and removal of inflammatory cells from the distal alveolar cavity. Except prone position ventilation in certain patients and low tidal volume ventilation [8,9], the overall effective management of ARDS is limited. At present, there is still no available medicine for ARDS yet. However, numbers of clinical trials and preclinical validation studies are in progress. As the mesenchymal stem cells (MSCs) therapy shows promising result in recent studies, it appears an attractive approach in ARDS therapy.

There is a rising of studies, both *in vitro* and *in vivo*, suggesting that stem cells from the adult tissue are engaged in both repair and regeneration of organs, e.g. bone fracture [10], type I diabetes mellitus [11], Crohn's diseases [12], and myocardial infarction [13]. Studies of influenza infected mouse models showed that mice treated with stem cells were more likely to survive and had normal lung histology after three to five months, while in the control group, bronchiolar of mice suffered infection, and the alveolar cells presented extensive inflammation and hemorrhagic edema [14]. Considering few clinical trials using MSC in ARDS therapy were undertaking, cell-based therapy seems to be a promising regiment in future respiratory medicine [15].

Depending on their source, stem cells can be divided into embryonic and adult stem cells. For ethical and safety, most of the researches focus on adult stem cell therapy. Over the past years, a variety of bone marrow-derived cells have been found to differentiate into airway and even alveolar epithelial cells, including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), multipotent adult progenitor cells (MAPC), and other populations [16]. Among them, MSCs is one of the most suitable cellular therapeutic strategy due to their accessibility, differentiation potential into lung tissues, immunomodulatory ability and regeneration properties [17,18]. They also have excellent safety record and the ability of treating various kinds of diseases in animal models [19]. This review focuses on the mechanisms of MSCs in ARDS, and technical protocol for cell based therapy.

History and Definition of MSCs

Stem cells were first discovered by Friedenstein [20,21], who defined the bone marrow osteogenic stem cells and found their high potential as proliferation and ability as common bone precursors and cartilage-forming cells. Caplan et al. [22] first used the name- mesenchymal stem cell, to define cells responsible for formatting and repairing bone and cartilage. Recently, results of meta-analysis from MEDLINE, EMBASE, BIOSIS and Web of Science have shown that MSCs substantially reduce the odds of death in animal models of ALI [23].

Mesenchymal stem cells (MSCs), also called skeletal stem cells or bone marrow stromal stem cells, are plastic adherent, non-hematopoietic cells that possess self-renewal and multi-lineage differentiation capacity [24]. MSCs are also derived from many kinds of tissues like bone marrow, adipose tissue, and placenta. The International Society of

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Cellular Therapy in 2006 defined MSCs based on three criteria: (1) they must be adherent to plastic under standard tissue culture conditions; (2) they must express certain cell surface markers such as CD73, CD90, and CD105, but must not express CD45, CD34, CD14, or CD11b; and (3) they must have the capacity to differentiate into mesenchymal lineages including osteoblasts, adipocytes, and chondroblasts under *in vitro* conditions [25].

Isolation and Differentiation of MSCs

As is explained in definition, MSCs are plastic adherent cells which express a variety of surface markers, such as CD44, CD63, CD105, CD146. The nature of this plastic adherence can be used to identify and isolate MSCs [26]. Based on these surface markers, recent studies isolated MSCs [27] by exploring DNA microarrays that define a set of biomarkers for *in vivo* bone-forming capacity and "stemness" [28]. MSCs from different tissues exhibit distinct molecular phenotype and differentiation potential, which has been reported in umbilical cord, adipose tissue, skeletal muscle, periodontal ligament and even brain [29-31]. However, only bone marrow-derived MSCs [32] have demonstrated the ability to form tissues *in vivo* [33], while more evidence of MSCs from other tissues is still needed. Meanwhile, MSCs can differentiate into and recruit several types of lung tissues with great potential. Given their efficiency in cell therapeutics, it is necessary to find out molecular mechanisms about how lineage-specificity controls differentiation. For example, studies show that Runx2 and PPARγ are expressed by osteoblastic and adipocytic lineages, respectively. And expression of these transcription factors is regulated by micro-environmental conditions including hormonal, growth factors, and mechanical forces. They induce a number of intracellular signaling pathways mediating the effects on transcription factors. In addition, the role of non-coding RNAs like miRNAs may regulate the expression and function of transcription factors that determine the differentiation fate of MSCs [34]. Also, derivation and purification of MSC contribute to the effect of treatment in animals [35]. Many experiment focused on the source of bone marrow while some novel trials found human umbilical cord-derived MSC [36].

Administration Method of MSCs (Table 1)

In animal studies, intratracheal route and intravenous route are two main delivery administrating method for MSCs therapy [6]. Appropriate method depends on the animal models and the most optimal method remains unclear. The experiments with *E. coli* endotoxin or bacterial induced model of acute lung injury(ALI) often delivered MSCs intratracheally [37,38]. Studies using bleomycin-induced [39], ischemia reperfusion-induced [40], ventilator-induced [41] and part of lipopolysaccharide(LPS)-induced [42] lung injury models administrated intravenously. Interestingly, Qin et al. [43] invented a novel method which was intra-pleural delivered. However, for practical reasons, intravenous administration is similar to clinical use and it is not easily to deliver cells into bronchia in patients with ARDS.

The way of administration may alter the timing of effect. In LPS-induced ALI models, beneficial time of MSCs through intratracheal delivery were less than 3 days while the time of effects were longer when MSCs were given intravenously. Of note, the timing of administration was within 6 h following ALI.

In ALI models of mice, as Zhu etc. summarized, the mean dose of MSCs typically was 29.9~10^6 cells/kg BW, and in rats it was 20.3 ~10^6 cells/kg BW, suggesting that the mean dose of MSC in ALI models in rodents typically ranges from 20 to 30 × 10^6 cells/kg BW [6]. Although many believe that higher doses will give a prolonged response, no actual dose response has been reported in the literature. However, no dose response study has been yet published.

Safety of MSCs and updated progress of MSCs therapy in ARDS

Before clinical use of MSCs, their safety should be evaluated firstly. At present, a plenty of clinical trials of MSCs have been conducted on different diseases [44]. In addition, MSCs have been tested, with no apparent major adverse effects. According to these clinical trials for usage of MSCs, no safety issues have arisen, and no potential concerns of tumor or ectopic tissue formation have been reported. A commercial MSC preparation showed no serious adverse events (SAEs) in a phase I trial and a phase II study in patients of Crohn's disease [45]. Currently, a phase III trial has been approved by FDA for its therapeutic usage for Crohn's Disease [46]. Recently, a randomized, multi-center test of systemic MSCs use for COPD treatment showed no adverse effects or pulmonary function impairment [47].

Potential efficacy and safety of MSCs administration for the treatment of ARDS had been demonstrated in pre-clinical studies, including experiments in animals and in ex vivo perfused human lung models [48,49]. Recently, a study tested allogeneic adipose-derived human MSCs in 12 patients with moderate to severe ARDS and reported no infusion-related adverse events but the clinical effect with the doses of 1 million cells/kg MSCs was minor [50].

In a phase I clinical trial of MSCs in ARDS patients, no specified events or treatment-related adverse events were reported, and none of the SAEs were thought to be MSC-related [51]. In this study, bone marrow-derived human MSCs was well tolerated in nine patients with moderate to severe ARDS [51]. More researches are being conducted to determine long-term safety of MSCs.

However, limited number of MSCs homing to injured tissues still existed in many experiments [52,53]. Besides the ability of expression of chemokine receptors and adhesion molecules to mediate homing of leukocytes to inflamed tissues [54], precise role of MSCs homing is still under investigation. Also, the optimal dose of MSCs remained unclear. Highest dose of 10 million MSCs/kg demonstrated more efficient in severe lung injury in sheep [55] and this dose was well tolerated in 9 patients with moderate-to-severe ARDS [56], it remained uncertain whether the dose was optimal or not. Further studies were warranted to figure out the details of MSCs therapy.

Mechanism of MSCs

MSCs based therapy is thought to be a potential novel strategy for ARDS for a number of reasons. Firstly, MSCs are multi-potent cells with the ability of inflammation inhibition and immunomodulation. Mean MCSs are also capable of secreting multiple paracrine factors including KGF, Ang-1. They also have ability to serve as the vehicle of gene therapy, which may enhance ability of MSCs in lung injury repair in ARDS.

MSCs inhibit inflammatory factors and regulate the immune system

MSCs, which secrete a variety of active molecules, including cytokines, growth factors, anti-inflammatory peptides, and antimicrobial peptides, present significant immunity effects. They suppress activation of lymphocytes and secretion of inflammatory

	ALI model/ARDS	Delivery route	Dose(x10(6)/animal)	Mean dose(x10(6)/kg)	PMID
Rats (200-300 g)	LPS-induced injury (intraperitoneal)	Intravenous	2	6.67-10	23289000
		Left thigh muscle	2	6.67-10	20664529
		Intrapleural	1	3.33-5	22697354
	Paraquat (PQ) poisoning	Intravenous	10	33.3-50	23257085
					23902576
	Ventilator-induced lung injury.	Intratracheal	4	13.3-20	23377221
		Intravenous	2	6.67-10	22106021
	Acute pulmonary ischemia-reperfusion (IR) injury	Intravenous	1.5	5-7.5	21781312
	Burn Induction	Thigh muscle	2	6.67-10	20573305
	Bleomycin (BLM)-induced acute lung injury	Intravenous	1	3.33-25	20137099
					18589176
Mice （30-35 g）	LPS-induced injury(intratracheal)	Intratracheal	0.75	21.4-25	17641052
					23360775
			0.25	7.13-8.33	23023971
			0.5	14.26-16.66	21569482
			1	28.52-33.33	21691076
		Intravenous	1	28.52-33.33	23760104
		Jugular venous canula	0.25	7.13-8.33	17803352
	intraperitoneal	Intravenous			
			0.5	14.26-16.66	17416739
			1	28.52-33.33	23760104
	Escherichia coli-induced acute lung injury	Intratracheal	1	28.6-33.3	21843339
					20945332
	Bleomycin (BLM)-induced acute lung injury	Intravenous	1	28.6-33.3	23207668
					19497992
	P. aeruginosa	Intravenous	1	28.6-33.3	22427530
	Polidocanol	Intratracheal	1	28.6-33.3	19606934
	Cecal ligation and puncture	Intravenous	1	28.6-33.3	19098906
Rabbits （2 kg）	Early stage of smoke inhalation injury	Intravenous	10		25214973
Sheep(30-40 kg)	*Pseudomonas aeruginosa*	Intravenous		5-10	24891325
Humans' clinical trial	ARDS	Intravenous		1-10	24708472

Table 1: Studies including animal models and clinical trials in ARDS with MSCs treatment.

factors (TNF-a, IFNc), and induce the release of anti-inflammatory factors (IL-10, IL-4) [57-59]. These effects increase the clearance of alveolar fluid and reduce inflammation, thus reverse the lung injury [60,61]. In addition to releasing soluble anti-inflammatory factors, the MSCs transfer microvesicles containing mitochondria, protein, and microRNA to other cells [62]. Inflammatory cytokines are thought to contribute to diffuse alveolar damage (DAD), in part by disrupting endothelial functions at capillary-alveolar junction, which leads to junction breaching, type II cell dysfunction, and surfactants loss. LPS-induced ALI model shows that after 24 h of MSC administration, the systemic inflammation is reduced because of many kinds of inflammatory mediators [63]. Studies also show that endothelial FoxM1 induces vascular repair as well as inflammation reduction [64]. Additionally, MSC reduced mortality in a mouse model of gram-negative peritonitis and sepsis, and the improvement in bacterial clearance was mediated through enhancement of phagocytic activity of peripheral blood mononuclear cells [65]. Furthermore, analysis of expression of major antimicrobial peptides indicates that one of the factors responsible for the antimicrobial activity of MSC against Gram-negative bacteria is human cathelicidin antimicrobial peptide, hCAP-18/LL-37 [37].

Importantly, MSCs can modulate innate and adaptive immune cells. First MSCs promote repolarization of monocytes and macrophages from type 1 to type 2 phenotype, which is characterized by high level of interleukin-10 secretion. Interleukin-10 blocks polymorphonuclear neutrophil influx into the injured tissue and prevents further damage [35,66-69]. Second, MSCs own the ability of interfering with dendritic cells differentiation, maturation and function, by skewing them towards a regulatory phenotype and decreasing their capacity to induce T cells activation. Third, they also impair cytotoxic activity, cytokine production and granzyme B release of natural killer cells [70,71]. Fourth, MSCs suppress T cell activation and proliferation and decrease their response by shifting them from Th1 to Th2 immune response [72]. Moreover, MSCs have been shown to inhibit the differentiation of naive T cells into Th17 cells and prevent the

secretion of pro-inflammatory cytokines by Th17 cells [73]. MSCs also promote induction of immunosuppressive T regulatory cells partially by reprogramming Th17 cells into T regulatory cells [35,74,75].

Restoring the integrity of pulmonary vascular barrier

More recent data suggest that factors released by MSCs influence the balance of permeability of alveolar-capillary induce leak of endothelial fluid [76,77]. Some reports of animal experiments describe that intrapulmonary MSC administration method can improve survival rate, by reducing pulmonary edema formation [48] and promoting repair of epithelium and endothelium [78]. Researchers have compiled adult stem cell therapy of the main clinical and experimental researches, which suggests that MSC on lung development and repair and remodeling of the beneficial effects and the side of secreted factors can effectively reduce inflammation and promote tissue repair [79]. And these factors have been evident in cultured human alveolar epithelial cells [80], which helped to restore the integrity of pulmonary vascular barrier. Furthermore, circumstantial evidence of humans and mice shows that ARDS may trigger the regeneration of pulmonary tissue. Meanwhile, the stem cells may play a role in this remarkable process, which yielded a defined set of cloned human airway stem cells marked by p63 expression [81].

Mechanisms may also involve the protection and repair of the epithelial barrier. MSCs releases angiogenesis -1 that prevents formation of actin stress fibers and disorganization of claudin 18, which is closely connected with the function to destroy epithelial cells, induce S1P and inhibit the internalization of endothelial VE-cadherin, through suppression of NF-κB activity. In experiment, stem cells use connecxin (connexin-43–based gap junctional channels) to attach to the walls of the alveoli and then translocate alveolar epithelial cell mitochondria damaged by endotoxin, thus help alveolar ATP generation, surface active agent production, and epithelial barrier restoration [62]. In addition, refilling the lost lung cells can restore the function of lung in the short term [82]. Researchers observed that cell therapy resulted in hyperplasia of type II cells and repair of the damaged epithelium [83].

Alveolar fluid reabsorption is based on sodium and chloride channels of the alveolar epithelial cells, injury of which is related to the epithelial cell damage, necrosis and apoptosis, caused by ARDS. Recovery of alveolar fluid reabsorption mainly depends on reconstruction of the epithelial barrier using new alveolar epithelium produced by alveolar type II epithelial cells. There is the evidence that primitive cells from the junction of bronchial cells promote the activation of repair device; the expression of alpha beta 64 - primitive cells [84] and c-kit + lung stem cell 204 is involved in this case. Some studies found that endothelial FOXM1 mediated bone marrow progenitor cells and induced inflammatory vascular repair after lung injury by restoring its integrity and accelerating the dissipation of inflammation [64].

MSCs engraftment in epithelium and recruitment in endothelial cells

Intravenous infusion is an ideal method of MSCs administration because it makes cells entrapped in lung capillary beds [85]. In addition, MSCs have the ability to transport to the inflammatory sites and migrate through the injured endothelium into the lung tissue, which is crucial for the treatment of ARDS [86]. This situation is driven by the connection between the chemokines released by injured sites and the receptors expressed by MSCs. While both embryonic and adult stem cells can be induced to express phenotypic markers of airway and/or alveolar epithelial cells *in vitro*, engraftment of airway or alveolar epithelium by stem or progenitor cells following systemic administration is rare and of unclear physiologic or therapeutic significance [15,16,87]. Nevertheless, MSCs respond, migrate, and facilitate repair of damaged tissue making them an attractive candidate for both prevention and treatment of lung disease.

The mechanisms of engraftment are not well understood. Both *in vitro* and *in vivo* experiments showed that the fusion of stem cells with other cells might be one approach. Other studies suggested that stem cells might acquire phenotypes of epithelial cells, which express markers induced by soluble factors from injured lung epithelium, possibly activated by Wnt/β-catenin pathway [89,90] or JNK-P38 signaling pathway [91]. One recent study showed that phenotypic change is induced by the release of membrane-derived microvesicles, which mediate communications between cells by transferring miRNAs [92,93]. Moreover, recent study showed transplantation of MSCs could improve lung injury through increasing autophagy-related signaling molecules. This result supports the hypothesis that MSCs stimulate autophagy in OGD-injured HPMVECs, at least in part via the PI3K/Akt signalling pathway[94,95].

Circulating or systemically administered stem or progenitor cells can be recruited into lungs and many of them initially localize in injured lung tissue [96-98]. In the meantime, the timing of cell administration after lung injury affects their recruitment and differentiation. Also, systemic administration of MSCs 4 hours after lung injury resulted in apparent engraftment as epithetical and endothelial cells [96] while administration at the later time resulted in engraftment as interstitial cells [96,99]. MSCs can secrete angiopoietin-1, which is a soluble factor capable of improving endothelial permeability and enhancing the endothelium survival and the vascular stabilization [100]. Meanwhile, MSCs inhibit the inflammation and preserve the integrity of vascular endothelium in the lungs after hemorrhagic shock [101].

Paracrine-modulating factors and KGF (Table 2)

It was firstly demonstrated by observing that systemic administration of MSCs were able to inhibit expression of several inflammatory cytokines in models of ALI [102]. In LPS-induced ARDS, 24 h after MSCs administration, inflammatory response was reduced because of release of the anti-inflammatory factors [63]. Interestingly, similar results were observed while only the medium of MSCs was used [49]. Despite the presence of MSCs in injured place, MSCs exert paracrine actions, secreting growth factors and cytokines. Indeed, paracrine-modulating factors secreted by MSCs seem to contribute to injury repair rather than MSC engraftment [81]. Several studies identified that the level of engraftment in the lung is limited, and *in vivo* studies showed limited replacement of injured tissue. Several studies identified that the level of engraftment in the lung is limited, and *in vivo* studies showed limited replacement of injured tissue. Therapeutic effects were attributed to paracrine, which is an ability to secrete soluble factors that modulate immune responses [103], and only a small number of pulmonary MSCs engraftment was observed [83].

Low levels of MSC cell engraftment and an even greater preventative effect of delivery of cell-free MSC-conditioned media support the importance of paracrine effect. So, to strengthen immune modulation, a variety of studies use these cytokines obtained from MSC cultures in hypoxia condition instead of MSCs. These media, including interleukin (IL-6 and IL-1) and growth factors (FGF-2, FGF-7, and VEGF-A), were found to promote attenuation of inflammatory response and stimulate endothelial cell migration, contributing to repair of vascular tissue

in an ischemic muscle injury model [104]. Meanwhile, MSCs secrete chemokines and growth factors (TGFB, TSG6, PGE2) that stimulate endogenous/resident cells, exhibit anti-apoptotic and immuno-modulatory effects as well as enhance vascular genesis [105,106] and the stimulation of all these secreted factors triggers the role of epithelial cell repair [107]. Moreover, recent *in vivo* studies showed a novel mechanism in which micro-vesicles released from MSC deliver messenger RNA (mRNA), micro RNA or proteins that reprogram the injured cells or induce secretion of cyto-protective factors, which has been demonstrated in ALI [108]. Above all, while systemically injected MSC can be entrapped in the lungs [109,110], they still make a positive influence through secretion of factors [111].

Secretion of paracrine factors that can regulate lung permeability and decrease inflammation by MSCs, is thought to be exerted in the treatment of ARDS. Keratinocyte growth factor (KGF), the role of which in acute lung injury has been studied since 1990s, has been extensively used in ARDS. Its characteristic of being stimulated by inflammatory cytokines and up-regulating the expression of the epithelial repair, may be one of the possible mechanisms for the MSCs treatment of ARDS, with consistent findings from other studies [112].

In animal studies, KGF reduces lung injury and increases the proliferation and repair of epithelial cells. Many studies demonstrated that KGF up-regulates the expression of epithelial sodium channel gene and enhances Na-K-ATPase activity to increase alveolar fluid clearance [113]. In addition, KGF increases the concentrations of anti-inflammatory cytokines IL-1ra and epithelial repair medium (MMP-9) in alveolar, and enhances macrophage function in necrotic cells and bacteria (GM-CSF) scavenging [114]. KGF mediated effects were not only found in animal models but also in clinical trials. Phase II clinical trials in Britain found that compared with the placebo group, KGF can increase the oxygen indexes of ARDS patients [115].

Similar to KGF, KGF-2, also named FGF-10 (fibroblast growth factor-10), is the heparin-binding protein expressed by MSCs, which binds to FGF receptor 2-IIIb expressed on epithelial cells. KGF-2 mediates interactions between epithelium and MSCs, which is crucial for lung development [116,117]. KGF-2 also prevents lung injury [118-120]. Furthermore, KGF-2 has no *in vitro* or *in vivo* effects on epithelial-like tumors [121], which validates the safety of KGF-2. Studies assessed the possibility of exogenous KGF-2 through directly *in vivo* experiments. Intratracheal administration of KGF-2 attenuates lung injury induced by LPS, suggesting that KGF-2 may reduce acute lung injury [122]. And pre-treatment with KGF-2 showed improvement of lung edema and inflammation compared with high-volume zero positive end-expiratory pressure (HVZP) alone, suggesting that KGF-2 might be considered as a promising prevention for human ventilator-induced lung injury (VILI) or other acute lung injury diseases [123]. Most recently, MSC-derived microvesicles have been found to protect LPS-induced ALI through delivering KGF mRNA into the injured alveolus [124]. Also, recent study showed a novel mechanism of KGF-2 that could easily isolate the lower respiratory tract of rats to lung-resident MSCs (LR-MSCs). Additionally, they illustrated that the LR-MSCs isolated from KGF-2 pretreated rats were protective against LPS-induced acute lung injury. Collectively, KGF-2 plays an important role in LR-MSCs proliferation and mobilization and in the organ specific protective effects against acute lung injury [125].

Endothelial and epithelial growth factors	Immunomodulation	Anti-inflammation and antimicrobial peptides	Reduction of alveolar epithelial permeability
FGF-10	IDO	IL1RN	ANGPT1
KGF	NO	ANGPT1	KGF
HGF	PGE2	KGF	HGF
IL-6	TGF-b	HGF TSG-6 LL-37	Lipoxin-A4

Table 2: Variety of active factors secreted by MSCs.

Gene therapy

MSCs have ability to serve as the vehicle of gene therapy in treatment of ARDS due to adhesion and proliferation properties [126]. Researches indicated that MSCs could deliver gene through viral vector based transplantation. While MSCs were transduced and maintained their own characteristics, including accessibility, proliferation and compatibility, it could be an ideal carrier to transfer gene to target tissues. Many studies demonstrated that transduced MSC could engraft and differentiate into lung epithelial cells with target gene expression [39,76,127]. Also, together with other types of cells, MSC could fuse with one of them to form a heterokaryon, converting its gene expression patterns to that fusion partner [128]. An experimental study found that 20–50% of lung epithelial cells derived from such cell fusion [129].

Additionally, combination of gene therapies showed further improved efficiency compared to use MSC alone. For instance, in an ALI model, administration of MSCs transfected with angiopoietin-1 improved alveolar inflammatory and permeability result, comparing with MSCs alone [76,80]. Furthermore, an *in vivo* mouse model showed that the LPS-induced lung injury was remarkably improved in the group treated with MSCs carrying FGF2 (MSCs-FGF2), including reduced histopathological index and level of inflammatory cytokines, suggesting that MSCs and FGF2 have a synergistic effect [130]. Although macrophages play a role in ARDS, the MSCs only weakly modulate macrophage function. However, researchers found MSCs stably transfected with a vector expressing negative inhibitor of CCL2 could induce macrophage activation. This experiment showed that MSCs can be used for drug delivery. Moreover, MSC-based endothelial locus-1 gene therapy has been established [131], which may enhance ability of MSCs repairing lung injury in ARDS [132].

Conclusion

ARDS has been studied so far for more than 40 years in epidemiology, risk factors, pathogenesis, diagnosis, treatment and prognosis. In spite of important developments of novel therapies, the mortality of ARDS is still high due to the complexity of the disease itself. Thus, ARDS becomes one of the leading lethal diseases in respiratory field. Exploring new treatments options based on pathogenesis is the future direction of ARDS research. Stem cells, especially MSCs, are the state-of-art progress of recent researches in ARDS. The mechanisms of MSCs therapy includes reducing inflammation, repairing lung tissue and the paracrine ability. Given the current findings, a promise is held for new breakthroughs in ARDS by cell based therapy.

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