Chapter 6
Challenges of Cell Therapy for Lung Diseases and Critical Illnesses

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Abbreviations

ARDS	Acute respiratory distress syndrome
CCL2	Chemokine ligand 2
COPD	Chronic obstructive pulmonary disease
eNOS	Endothelial nitric oxide synthase
EPC	Endothelial progenitor cell
GMP	Good manufacturing process
HGF	Hepatocyte growth factor
IDO	Indoleamine 2,3-dioxygenase
IFN-β	Interferon beta
IL-10	Interleukin 10
IL-6	Interleukin 6
IND	Investigational new drug
IPF	Idiopathic pulmonary fibrosis
ISCT	International Society for Cellular Therapy
KGF	Keratinocyte growth factor
MIP-2	Macrophage inflammatory protein 2-alpha
miRNA	Microribonucleic acid
MSC	Mesenchymal stromal (stem) cells
NHBLI	National Heart Blood and Lung Institute

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NO	Nitric oxide
PACT	Production Assistance in Cellular Therapies
TGF-β	Transforming growth factor beta
TNF-α	Tumour necrosis factor alpha
TRAIL	Tumour necrosis factor-related apoptosis-inducing ligand

6.1 Introduction

Pulmonary diseases, including acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), bronchopulmonary dysplasia, and occupational diseases such as silicosis, remain important causes of morbidity and mortality worldwide. Some of these, such as COPD and asthma, in contrast to many other major diseases, are increasing in prevalence. COPD, the fourth leading cause of disease mortality worldwide, is expected to be the third by 2020, and thus remains a major public health concern. Current available treatments for lung diseases may lessen the severity of symptoms, but there is still a pressing need for new therapeutic approaches, since no existing treatment has been shown to reduce disease progression, reverse the pathological changes, and restore the organ functionality. Lung transplantation is considered the only curative approach for end-stage chronic diseases; however, there is a significant shortage of suitable donor lungs and many on waiting lists die before a lung becomes available. Further, lung transplantation requires lifelong immunosuppression and five-year mortality after transplantation is approximately 50 %. Lung transplantation is also not a realistic option for patients in many parts of the world. New therapeutic approaches are thus desperately needed (Weiss 2014).

Approaches utilizing cell-based therapies for lung diseases have progressed rapidly in recent years. Systemic or local (intratracheal) administration of different stem and progenitor cell types has been demonstrated to have efficacy in different pre-clinical models of lung diseases (Weiss et al. 2013a, b; Kotton 2012; Lau et al. 2012). The different cell types have included endothelial progenitor cells (EPCs), bone marrow-derived mononuclear cells, amniotic fluid cells, and mesenchymal stromal (stem) cells (MSCs) (Weiss 2014; Weiss et al. 2013a, b). However, the majority of available pre-clinical data have focused on investigation of MSCs.

6.2 Mesenchymal Stromal (Stem) Cells

MSCs were first described in 1968, and since then, have been widely investigated for their applications in stem cell-based regeneration studies. The nomenclature has evolved over time as MSCs were initially named fibroblastic colony-forming units, subsequently as marrow stromal cells, mesenchymal stem cells, mesenchymal stromal cells, or as multipotent mesenchymal stromal cells. Nowadays, the application of the more commonly currently utilized terms, mesenchymal stem cell or

mesenchymal stromal cell, is inconsistent in the literature. This nomenclature loosely depends on whether MSCs are being used for their ability to differentiate into lineages potentially useful in regenerative medicine efforts and structural repair, or utilizing their immunomodulatory properties in the absence of structural engraftment (Lotfinegad et al. 2014).

MSCs are described as self-renewal, fibroblastoid, non-phagocytic, adherent cells which are able to differentiate in vitro into some cell lineages, in particular, culture systems (Mafi et al. 2011; Paunescu et al. 2007; Oswald et al. 2004; Tran et al. 2011). In addition to the bone marrow (Li and Ikehara 2013; Kern et al. 2006), MSCs have been found in other sources, including liver (Najimi et al. 2007), lung (Sabatini et al. 2005; Lama et al. 2007), brain (Kang et al. 2010), adipose tissue (Kern et al. 2006; Pawitan 2009; Zuk et al. 2002; Zannettino et al. 2008), peripheral blood (Chong et al. 2012), cornea (Choong et al. 2007), synovium (Jones et al. 2010), thymus (Krampera et al. 2007), dental pulp (Gronthos 2011; Gronthos et al. 2000), periosteum (Nakahara et al. 1990), tendon (Bi et al. 2007), fallopian tube (Jazedje et al. 2009), placenta (Sabapathy et al. 2012; Igura et al. 2004), amniotic fluid (You et al. 2008), Wharton's jelly (Wang et al. 2004), umbilical cord (Capelli et al. 2011; Romanov et al. 2003), and umbilical cord blood (Kern et al. 2006).

However, definition and investigation of MSCs continue to be confounded by several issues. For instance, there can be important differences in MSC properties, such as cell surface epitopes, secretome, immunomodulatory properties, lineage tendencies, and genomic stability, according to the tissue, strain, and species that MSCs are derived from (Keating 2012; Prockop and Oh 2012a, b; Romieu-Mourez et al. 2012; Baer and Geiger 2012). Further, there is growing evidence that MSCs are heterogeneous and that different MSC subtypes exist, even in cells isolated from the same source. Thus, delineating functional differences between MSCs isolated from different sources is an area of current intense investigation (Viswanathan et al. 2014).

To foster a more uniform characterization of MSCs and facilitate the exchange of data among investigators, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) have proposed minimal criteria to define human MSCs, which are listed as: (1) MSCs must be plastic-adherent when maintained in standard culture conditions; (2) MSCs must express CD105, CD73, and CD90 in at least 95 % of cell population, and lack expression of CD45, CD34, CD14 or CD11b, CD79 alpha or CD19, and HLA-DR surface molecules as measured by flow cytometry; (3) MSCs must differentiate into osteoblasts, adipocytes, and chondroblasts in vitro (Dominici et al. 2006; Horwitz et al. 2005). These criteria are currently being updated given the continued advances in understanding MSC biology with particular focus on developing potency assays applicable to clinical applications (Viswanathan et al. 2014). To address some of the variations in properties of cultured MSCs, an NCRR/NIH-sponsored Center for Preparation and Distribution of Adult Stem Cells (MSCs) serves as a pre-clinical resource for standardized preparations of mouse, rat, and human MSCs (http://medicine.tamhsc.edu/irm/msc-distribution.html). The NHBLI also sponsors the Production Assistance in Cellular Therapies (PACT) program, a training and GMP manufacturing resource that supports pre-clinical, IND preparation, and clinical investigations with MSCs and other cell therapy (https://secure.emmes.com/pactweb/Facilities).

6.3 Mechanisms of Action

While therapeutic interest in MSCs initially focused on exploring their capacity for multilineage differentiation to directly regenerate tissues and organs (Pittenger et al. 1999; Caplan and Bruder 2001), they are now also viewed as potent immunomodulators of disease-associated tissue microenvironments (Caplan 2009). Thus, the current translational landscape for MSCs includes therapeutic models involving direct tissue regeneration as well as indirect, through their anti-inflammatory and immunomodulatory effects on damaged and diseased tissues (Bianco et al. 2013; Griffin et al. 2013; Le Blanc and Mougiakakos 2012; Prockop and Oh 2012a, b) (Fig. 6.1). The capacity of MSCs to broadly modify the activity of most major components of the innate and adaptive immune system is now seen, along with their pro-angiogenic and cytoprotective effects, as an essential component of their therapeutic potential for many disease targets (Caplan and Bruder 2001; Bianco et al. 2013; Griffin et al. 2013; Le Blanc and Mougiakakos 2012).

The mechanisms by which MSCs might alleviate inflammation and injury are not completely understood and, as in other organ systems, likely involve multiple pathways including release of soluble mediators and/or microsomal particles as well as cell–cell contact. Importantly, the mechanisms of MSCs actions are different in different lung diseases and reflect the ability of the MSCs to sense and respond differently to different inflammatory environments (Weiss 2014; Weiss et al. 2013a, b). Much current interest in MSCs has focused on soluble factors due to their ability to secrete multiple paracrine factors such as growth factors, factors regulating

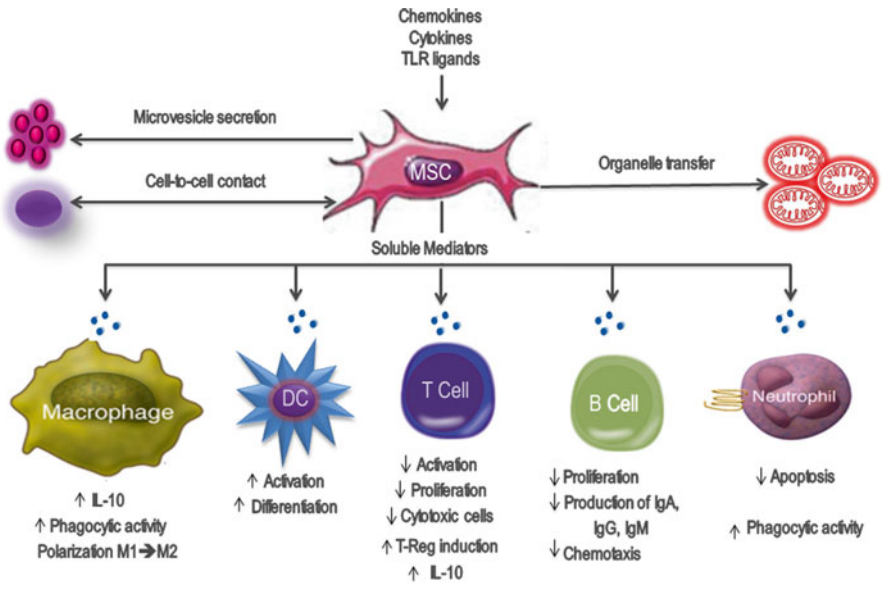

Fig. 6.1 Mechanisms of action of MSCs. MSCs promote benefitial effects through cell-to-cell interactions and through secretion of soluble mediators, microvesicles and whole organelles, that can directly affect many cells, regulating, for example, the innate and adaptative immune system

endothelial and epithelial permeability, factors regulating innate and adaptive immunity, anti-inflammatory cytokines, and more recently, antimicrobial peptides. Some of the soluble mediators implicated in the different model systems include IL-6, IL-10, indoleamine 2,3-dioxygenase (IDO), Nitrous Oxide (NO), hepatocyte growth factor (HGF), and transforming growth factor (TGF)-β (Lotfinegad et al. 2014). Transduction or transfection of the MSCs to over-express secreted mediators including angiopoietin-1 or keratinocyte growth factor (KGF) further decreases endotoxin-mediated lung injury presumably through abrogation of endotoxin-mediated endothelial injury (Xu et al. 2008; Chen et al. 2013). While native MSCs are effective, MSCs transduced to over-express eNOS, IL-10, KGF, or a CCL2 inhibitor were found to be more effective in preventing monocrotaline-induced pulmonary hypertension, ischemia-reperfusion-induced lung injury, or bleomycin-induced pulmonary inflammation and subsequent fibrosis, respectively (Prockop and Oh 2012a, b; Keating 2012; Weiss 2013; Antunes et al. 2014; Kanki-Horimoto et al. 2006). MSCs appear also to act in part by decreasing the increased endothelial permeability found in acute lung injury, by secreting antibacterial peptides, by promoting an anti-inflammatory M2 phenotype in alveolar macrophages, by increasing monocyte phagocytic activity, and by reducing collagen fiber content associated with increased metalloproteinase-8 expression and decreased expression of tissue inhibitor of metalloproteinase-1 (Weiss et al. 2013a, b). However, MSCs may not always ameliorate lung injury with some pre-clinical data suggesting that MSCs may contribute to established lung fibrosis (Epperly et al. 2003; Yan et al. 2007; Weiss and Ortiz 2013).

In addition, the ability to secrete microparticles that contain not only proteins but RNA or miRNA species which can modulate the expression of multiple genes make these packaging vesicles an attractive and quite plausible means for MSCs to regulate multiple pathways and produce a robust therapeutic effect in different lung injury models (Lee et al. 2012; Aliotta et al. 2012; Zhang et al. 2012a, b; Thebaud and Stewart 2012; Islam et al. 2012). Besides this, direct mitochondrial transfer from MSCs to ATII cells through connexin 43-mediated cell–cell bridges has been demonstrated to replenish endotoxin-depleted ATP stores and restore surfactant secretion (Islam et al. 2012).

Importantly, MSCs can also exert effects on lung inflammation and injury through primary interactions with the immune system rather than through direct actions in lung. For example, available information demonstrates that MSCs alleviate endotoxin-induced acute lung injury in mouse models inhibiting Th1 response through release of soluble anti-inflammatory, anti-bacterial, and angiogenic substances, including IL-10, angiopoietin 1, KGF, and others (Mei et al. 2007; Lee et al. 2009a, b; Danchuk et al. 2011; Gupta et al. 2012; Ionescu et al. 2012a, b). In contrast, MSC administration in mouse models of asthma (allergic airways inflammation) ameliorates airways hyper-responsiveness by reducing Th2/Th17-mediated inflammation through effects on antigen-specific T lymphocytes and by up-regulating T-regulatory cells (Cho et al. 2009; Park et al. 2010; Nemeth et al. 2010; Firinci et al. 2011; Goodwin et al. 2011). As such, as MSC-based therapies are developed for lung diseases, the specific disease pathogenesis in the context of the known actions of the MSCs must be carefully considered (Fig. 6.2).

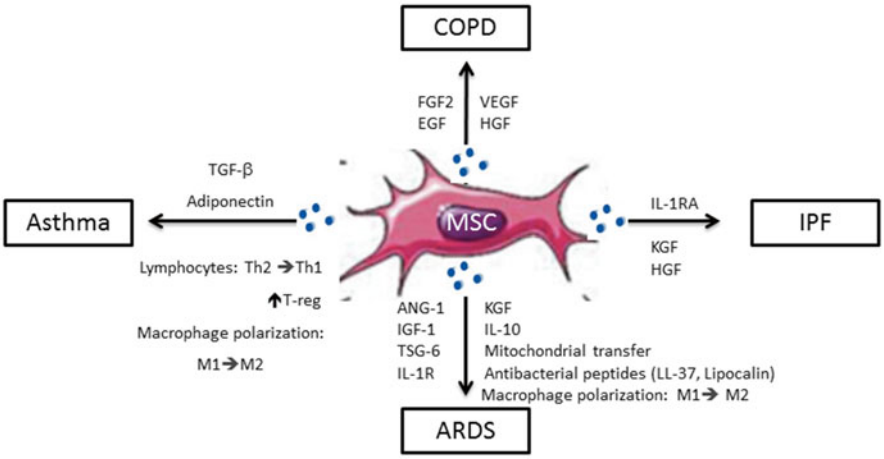

Fig. 6.2 MSCs trigger different responses according to each lung pathological environment. MSCs can secrete different soluble mediators depending on the lung disease microenvironment they get exposed to

6.4 Localization of MSCs in Lung After Systemic MSC Administration

Following systemic administration of MSCs isolated from bone marrow, adipose, placenta, or cord blood, a number of studies demonstrate that the cells initially localize in the lung vascular bed and that lung injury results in increased localization and/or retention of marrow-derived cells in lung (reviewed by Weiss 2013; Antunes et al. 2014). Whether this represents formation of cell emboli in the lung vasculature or specific adherence to pulmonary vascular adhesion or other molecules remains unclear. Further, the source of the MSCs may influence retention in the lung. For example, MSCs derived from human umbilical cord blood are cleared more rapidly from the lungs than are human bone marrow-derived MSCs (Nystedt et al. 2013). This reflects both differences in size of the MSCs from different sources as well as differential expression of specific integrin and proteoglycan patterns. Retention in the lung may also trigger the MSCs to have functional effects. For example, embolization of systemically administered MSCs in lung was felt to result in secretion of an anti-inflammatory protein, TSG-6 (Lee et al. 2009a, b). However, although bone marrow- or adipose-derived MSCs can be induced in vitro to express phenotypic markers of alveolar or airway epithelial cells, retention of MSCs in the lung is generally transient. Structural engraftment of MSCs as lung epithelium is a rare event of uncertain physiologic significance in lung (Loi et al. 2006; Sueblinvong et al. 2008; Ma et al. 2011; Maria and Tran 2011; Li et al. 2012; Yan et al. 2012; Baer 2011). However, some available data suggests that systemically administered MSCs can engraft as fibroblasts or myofibroblasts under certain fibrosing injury conditions, further discussed below (Antunes et al. 2014; Kanki-Horimoto et al. 2006). This is a potential undesirable effect of the MSCs.

6.5 Use of MSCs in Lung Diseases

A steadily increasing number of articles demonstrate efficacy of either systemic or intratracheal administration of MSCs obtained from bone marrow, adipose, cord blood, or placenta in a growing spectrum of lung injury models in mice and in a slowly growing number of clinical investigations in lung diseases (reviewed by Weiss 2013; Antunes et al. 2014). This includes mouse models of acute lung injury and bacterial lung infection (Gupta et al. 2012; Ionescu et al. 2012a, b; Danchuk et al. 2011; Kim et al. 2011; Sun et al. 2011a, b; Xu et al. 2012; Zhang et al. 2013), asthma (Firinci et al. 2011; Goodwin et al. 2011; Kapoor et al. 2011; Kavanagh and Mahon 2011; Lee et al. 2011; Ou-Yang et al. 2011; Ionescu et al. 2012a, b; Lathrop et al. 2014), bronchopulmonary dysplasia (Chang et al. 2011; Pierro et al. 2013; Zhang et al. 2010, 2012a, b; Tropea et al. 2012; Sutsko et al. 2013), COPD (Hoffman et al. 2011; Katsha et al. 2011; Schweitzer et al. 2011; Ingenito et al. 2012; Kim et al. 2012), ischemia re-perfusion injury (Yang et al. 2009; Manning et al. 2010; Sun et al. 2011a, b), post-inflammatory lung fibrosis (Ortiz et al. 2003, 2007; Rojas et al. 2005; Zhao et al. 2008; Aguilar et al. 2009; Kumamoto et al. 2009; Moodley et al. 2009; Cargnoni et al. 2010; Cabral et al. 2011; Lee et al. 2010; Saito et al. 2011), pulmonary hypertension (Lee et al. 2012; Baber et al. 2007; Umar et al. 2009; Kanki-Horimoto et al. 2006; Hansmann et al. 2012; Liang et al. 2011), sepsis and burns (Gonzalez-Rey et al. 2009; Nemeth et al. 2009; Iyer et al. 2010; Mei et al. 2010; Yagi et al. 2010a, b; Krasnodembskaya et al. 2012), and other critical illness or autoimmune-related lung injuries including hemorrhagic shock, lupus, pancreatitis, silicosis, and ventilator-induced lung injury (Shi et al. 2012; Pati et al. 2011; Wang et al. 2012; Lassance et al. 2009; Chimenti et al. 2012; Curley et al. 2012). Systemically administered MSCs can also home to tumors, through as yet unclear chemotactic mechanisms, and have been utilized for delivery of chemotherapeutic and other anti-tumor agents in mouse lung tumor models. This may provide a viable therapy for lung cancers, particularly with MSCs engineered to express anti-tumor compounds such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) or Interferon beta (IFN-β) (Kanehira et al. 2007; Rachakatla et al. 2007; Stoff-Khalili et al. 2007; Xin et al. 2007; Zhang et al. 2008; Matsuzuka et al. 2010; Loebinger et al. 2009a, b; Heo et al. 2011; Hu et al. 2012). MSC administration has also been demonstrated to alleviate inflammation and injury produced by intratracheal instillation of either endotoxin or bacterial in human lung explants (Lee et al. 2009a, b, 2013).

In parallel with robust pre-clinical data, a slowly growing number of clinical investigations of MSC-based therapy in different lung diseases including ARDS, COPD, IPF, and silicosis are occurring (Table 6.1). In the following sections, the rationale for potential MSC effects, available pre-clinical data, and considerations of clinical trials of MSCs in ARDS, COPD, IPF, and silicosis will be considered.

Table 6.1 Worldwide stem cell clinical trials on lung diseases. Brief description of study location, number of enrolled patients, source and dose of MSCs, frequency of injections, route of administration, follow-up length, study status and clinical trials registration number in clinicaltrials.gov

Disease	Location	Patients	Cell type	Dose	Frequency	Delivery	Follow-up	Status	ClinicalTrials.gov
ARDS	USA	69	BM-MSC	$1–10 \times 10^6$/kg	Single dose	Intravenous	12 months	Recruiting	NCT01775774
	USA	60	BM-MSC	1×10^7/kg	Single dose	Intravenous	12 months	Recruiting	NCT02097641
	China	12	AD-MSC	1×10^6/kg	Single dose	Intravenous	28 days	Recruiting	NCT01902082
	China	20	MEN-MSC	1×10^7/kg	Twice weekly for 2 weeks	Intravenous	14 days	Recruiting	NCT02095444
	Sweden	10	BM-MSC	[a]	[a]	[a]	12 months	Recruiting	NCT02215811
COPD	Brazil	4	BMDMC	1×10^8/ml	Single dose	Intravenous	12 months	Completed	NCT01110252
	USA	62	BM-MSC	1×10^8	Four monthly	Intravenous	2 years	Completed	NCT00683722
	Brazil	10	BM-MSC	[a]	Single dose	Endobronchial	4 months	Recruiting	NCT01872624
	Netherlands	10	BM-MSC	[a]	Twice weekly	Intravenous	8 weeks	Completed	NCT01306513
	Russia	30	BM-MSC	2×10^8	Every 2 months for 1 year	Intravenous	2 years	Recruiting	NCT01849159
	Iran	12	BM-MSC	6×10^7	Single dose	Endobronchial	1 year	Not recruiting	NCT01758055
	Mexico	30	AD-MSC	[a]	Single dose	Intravenous	6 months	Recruiting	NCT01559051
IPF	USA	25	BM-MSC	2×10^7	Single dose	Intravenous	60 weeks	Recruiting	NCT02013700
	Spain	18	BM-MSC	Escalating doses	[a]	Endobronchial	12 months	Recruiting	NCT01919827
	Australia	8	PL-MSC	$1–2 \times 10^6$/kg	Single dose	Intravenous	6 months	Not recruiting	NCT01385644
Silicosis	Brazil	5	BM-MSC	2×10^7/kg	Single dose	Endobronchial	6 months	Recruiting	NCT01239862

ARDS acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *IPF* idiopathic pulmonary fibrosis, *AD-MSC* adipose-derived mesenchymal stem cells, *BM-MSC* bone marrow-derived mesenchymal stem cells, *MEN-MSC* menstrual blood-derived mesenchymal stem cells, *PL-MSC* placental-derived mesenchymal stem cells

[a]Data not available

6.6 Acute Respiratory Distress Syndrome

The immunomodulatory and reparative potential of MSCs makes them potential therapeutic tools for the acute inflammatory response to infection and pulmonary injury seen in ARDS. Several pre-clinical studies on ARDS have demonstrated that MSCs may improve the pulmonary and systemic inflammation characteristic of the disease (Rojas et al. 2005; Nemeth et al. 2009; Mei et al. 2010; Gupta et al. 2007). In models of endotoxin- or bacterial-induced ARDS mice and in explanted human lungs, MSC administration not only attenuates inflammation by decreasing several inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), macrophage inflammatory protein 2-alpha (MIP-2), IFN-γ, IL-1β, MIP-1α, IL-6, IL-8, and keratinocyte-derived cytokine in plasma and bronchoalveolar lavage fluid, but it is also able to rescue epithelial cells with mitochondrial dysfunction by mitochondria transfer (Islam et al. 2012; Spees et al. 2006). In addition, MSCs favorably influence the host response to bacterial infections, the commonest and most severe cause of ARDS. MSC therapy can reduce bacterial counts via a number of mechanisms, including increased antimicrobial peptide secretion, such as lipocalin-2 (Gupta et al. 2012), and enhanced macrophage phagocytosis (Krasnodembskaya et al. 2012; Nemeth et al. 2009). MSCs also enhance repair following lung injury, as evidenced by the findings that both intravenous (Curley et al. 2012) and intratracheal (Curley et al. 2013) MSC therapy restore lung function following ventilator-induced lung injury via a KGF-dependent mechanism. Based on these promising preclinical findings, a number of early-phase clinical trials have begun to investigate the potential of MSC therapy for severe ARDS.

Currently, five studies of MSC therapy safety in patients with ARDS are listed in ClinicalTrials.gov. At the University of California, San Francisco, a phase I, multicenter, open-label dose escalation clinical trial is in progress to assess the safety of intravenous infusion of allogeneic bone marrow-derived human MSCs in ARDS (NCT01775774) and a phase II, multicenter study was initiated in March, 2014, to assess the safety and efficacy of a single dose of allogeneic bone marrow-derived human MSCs infusion in patients with ARDS. In Sweden, a phase I, multi-center, open-label, non-randomized controlled trial is also testing the safety of bone-marrow-derived MSCs in ARDS (NCT02215811). Two phase I, randomized, double-blind, placebo-controlled trials are also taking place in China to test the safety of systemic infusion of allogeneic human adipose MSCs (NCT01902082) and of MSCs derived from menstrual blood (NCT02095444) in ARDS patients.

6.7 Chronic Obstructive Pulmonary Disease

In several preclinical studies, MSC administration has been demonstrated to attenuate inflammation by decreasing levels of inflammatory mediators, such as IL-1β, TNF-α, IL-8, as well as decrease apoptosis (Huh et al. 2011; Zhen et al. 2010), improve parenchymal repair (increased levels of KGF, HGF, and epidermal growth factor),

and increase lung perfusion (Huh et al. 2011; Shigemura et al. 2006; Guan et al. 2013). Based on these preclinical findings, several groups are investigating the therapeutic potential of MSC therapy in COPD patients.

The first safety trial registered in ClinicalTrials.gov (NCT01110252) assessed systemic administration of autologous bone marrow mononuclear cells in four Brazilian patients/volunteers with advanced COPD (stage IV dyspnea) and found no obvious adverse effects after 1 year (Ribeiro-paes et al. 2011). In a recent trial carried out in the United States (NCT00683722), using non-HLA matched allogeneic bone marrow-derived MSCs obtained from healthy volunteers (Prochymal®; Osiris Therapeutics Inc), sixty-two patients were randomized to double-blinded intravenous infusions of either allogeneic MSCs or vehicle control. Patients received four monthly infusions (100×10^6 cells/infusion) and were subsequently followed for 2 years after the first infusion (Weiss et al. 2013a, b). This trial demonstrated that use of MSCs in COPD patients may be considered safe, as there were no infusion reactions and no deaths or serious adverse events deemed related to MSC administration. However, no significant differences were observed in the overall number of adverse events, frequency of COPD exacerbations, or severity of disease in patients treated with MSCs. A significant decrease was observed in circulating C-reactive protein in MSC-treated patients giving a potential mechanistic clue of MSC actions.

A phase I, non-randomized, open-label study in Brazil is currently recruiting patients diagnosed with severe heterogeneous emphysema to evaluate the safety of one-way endobronchial valves combined with bone-marrow MSCs (NCT01872624). Another phase I, non-randomized, non-blinded, prospective study to test the safety and feasibility of administration of bone-marrow MSCs before and after lung volume reduction surgery for severe pulmonary COPD has been concluded in the Netherlands (NCT01306513). Results for this study are pending. An open-label, non-randomized, multicenter study is currently underway in Mexico to evaluate the safety and efficacy of autologous adipose-derived stem cell transplantation in GOLD moderate-severe patients (NCT01559051).

6.8 Idiopathic Pulmonary Fibrosis

When administered early after injury is instituted, MSCs attenuate inflammation and prevent development of bleomycin-induced lung fibrosis in mice, the most commonly utilized experimental model. However, administration of MSCs at time intervals longer than 7 days after bleomycin administration had no effect on established fibrotic changes in either mouse or pig lungs (Ortiz et al. 2003). Further, using a different model of lung fibrosis induced by radiation exposure in rodents, MSCs administered at time points at which established fibrotic changes were present, MSCs were detected in the interstitium as myofibroblasts suggesting that fibroblastic differentiation of MSC occurred in response to mediators produced in the injured tissue (Epperly et al. 2003; Yan et al. 2007). These data suggest that MSC administration in the setting of an established or ongoing fibrotic response may worsen the

disease process and augment scarring in injured tissue rather than reversing it. As such, available data only supports a potential ameliorating effect of MSC administration in fibrotic lung diseases if administered early in the disease course during active inflammation (Weiss et al. 2013a, b). At present, there is no data to support an ameliorating effect of MSCs on established lung fibrosis. Thus, careful consideration must be given to clinical investigations of MSCs in fibrotic lung diseases.

Despite these concerns, there are three trials listed in ClinicalTrials.gov that are taking place to evaluate the safety and feasibility of MSC therapy in IPF patients. In the United States, a phase I/ll, randomized, blinded, and placebo-controlled trial is recruiting 25 IPF patients to investigate the safety, tolerability, and potential efficacy of intravenous infusion of allogeneic human MSCs (NCT02013700). Another phase I, open-label, multicenter, non-randomized study will evaluate the safety and feasibility of the endobronchial infusion of autologous bone-marrow MSCs at escalating doses in patients with mild-to-moderate IPF at Navarra University in Spain (NCT01919827). A third phase I, open-label, single-center, non-randomized dose-escalation study in Australia evaluated the safety and feasibility of placental-derived MSC infusion in IPF patients (NCT01385644). Initial results from this trial demonstrate no adverse effects over the 6-month follow-up period. A fourth trial, not listed in clinicaltrials.gov, reported no adverse effects of endobronchial administration of autologous adipose-derived MSCs over a 1-year follow-up period (Tzouvelekis et al. 2013).

6.9 Silicosis

Preclinical studies using an experimental model of silicosis demonstrated that both systemic and intratracheal administration of autologous BMMCs reduce inflammation and fibrosis (Lassance et al. 2009; Lopes-Pacheco et al. 2013). These positive effects encouraged a non-randomized, phase I trial of endobronchial administration of autologous BMMCs in patients with chronic and accelerated silicosis in Brazil (NCT01239862). In this study, three patients each received 2×10^7 bone marrow-derived cells labeled with 99mTc. The cellular infusion procedure was well tolerated by the patients, and no respiratory, cardiovascular, or hematological complications were observed. Scintigraphy showed an increase in lung perfusion in the basal region up to day 180 after the infusion, while the apex and midzone areas presented reduced perfusion at day 180 (Loivos et al. 2010; Souza et al. 2012). However, no subsequent clinical study of MSCs in silicosis has occurred.

6.10 Conclusions and Future Directions

Cell therapy approaches for lung diseases and critical illnesses including ARDS, COPD, IPF, and silicosis continue to evolve at a rapid pace. Pre-clinical studies with MSCs have generated a great amount of enthusiasm as a beneficial therapy for lung

diseases and critical illnesses. Initial clinical trials have demonstrated that MSC administration is safe, with few adverse effects, but substantial challenges still have to be overcome before MSCs can be used for clinical practice. As such, further studies focusing on understanding the mechanisms of action of MSCs must be more investigated in order to continue to develop rational approaches for clinical trials. Nonetheless, cell-based therapies with MSCs and other cell types offer potential hope for these devastating and incurable pulmonary diseases.

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