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Review

Stem cell therapy for lung diseases: From fundamental aspects to clinical applications

Hossein Hosseinirad[1], Mohsen Rashidi[2], Mehrdad Moosazadeh Moghaddam[1*], Hamid Tebyanian[1, 3*], Soheila Nouraei[4], Seyed Ali Mirhosseini[5], Mehdi Rasouli[6], Soheil Habibian[7]

[1] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2] Faculty of Medicine, Mazandaran University of Medical Sciences Department of Physiology and Pharmacology, Sari Iran
[3] Research Center for Prevention of Oral and Dental Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran
[4] Department of Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[5] Applied Microbiology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[6] Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tabriz, Iran
[7] Faculty of Veterinary Medicine, Islamic azad university, Karaj, Iran

Correspondence to: mm.genetics@gmail.com, tebyan.hamid@yahoo.com

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Abstract: The respiratory system is a complex group of organs in the human body, all of which are necessary in breathing. Due to its special anatomy and composition, after exposure to various damaging factors such as micro particles, carbon granules and toxic gases, the respiratory system can be affected by a variety of damage without return to its original state. Currently, the prevalence of lung diseases, including asthma, and chronic obstructive pulmonary diseases, such as emphysema, has increased remarkably. New therapeutic approaches are desperately needed to discover regenerative medicine approaches, especially cell therapy. This review summarizes the recent advances in stem cell treatments and the research efforts conducted through the application of stem cell therapy for respiratory system diseases. In particular, researchers have used animal models to gather data about treating lung injury by stem cell transplantation. This review concentrated on the findings about route, timing and adjustment of cell transplantation dose, optimum stem cell type selection and potency marker of cells as therapeutic agents. These factors are essential subjects for approval and clinical transplantation. The current clinical trials aiming at treatment of lung diseases by stem cells are mentioned and discussed.

Key words: Stem cell Therapy; Lung diseases; Respiratory system.

Introduction

Respiratory disease is a medical term that covers pathological conditions affecting the tissues and organs responsible for gas exchange in the body, and involves conditions of the nose, nasal cavity, pharynx, larynx, trachea, lungs, bronchi, bronchioles, alveoli and the nerves and muscles of breathing (1). Respiratory diseases range from mild and insignificant diseases, such as the common cold, to dangerous diseases, such as bacterial pneumonia, pulmonary embolism and, in their final stages, more complex illnesses such as acute asthma or lung cancer (2). Respiratory diseases impose a remarkable global healthcare burden. Current data show that 235 million people have asthma, at least 200 million suffer from chronic obstructive pulmonary disease (COPD), 65 million struggle with moderate-to-severe COPD, and more than 50 million people endure occupational lung diseases. At least 1 billion people suffer from chronic respiratory conditions and more than 2 billion people are threatened by toxic effects of biomass fuel consumption. In addition, 1 billion are living in outdoor polluted air and 1 billion have contact with tobacco smoke. Four million people die annually from chronic respiratory disease before reaching mature ages. COPD is the fourth leading cause of death worldwide. Lung cancer is considered the most deadly cancer in the world, causing death in more than 1.4 million people annually, and the number of cases is growing (3). Epidemiological data on respiratory diseases are very limited in the WHO's Eastern Mediterranean Region, including Iran. Both acute and chronic lung injuries involve different kinds of symptoms, ranging from mild and reversible changes, such as allergies, to severe and irreversible problems, such as asthma, fibrosis and chronic obstructive diseases. In most diseases affecting the airways, the epithelial linings of the airway are found to be at risk of irreversible damages that cannot naturally be repaired. Currently, lung transplantation and surgery are the standard treatment approaches (4,5). In many type of dysfunctions, the prolonged use of bronchodilators is effective, if the terminal airways or bronchioles have malfunctioned or are damaged. Long-term bronchodilator therapy can lead to major problems and safety concerns regarding these patients, and there is an urgent demand for a new therapeutic strategy to overcome these issues (6). Transplantation is hindered by a shortage of organ donors and severe surgical, technical and immunological complications, which urge innovative therapeutic approaches (7). One approach is grafting cell populations capable to regenerate and replace damaged lung and airway epithelia. Recently, the use of cell therapy to

treat pulmonary patients who failed to respond to common treatments has increased.

This review examined a series of recently published studies on the use of stem cells to restore and regenerate respiratory system tissues. Several studies have developed animal models using hematopoietic stem cells, endothelial and mesenchymal progenitor cells and embryonic cells, in efforts to generate functional cell types belonging to the respiratory system. In many cases, the affected lungs showed improvement after cell grafting. Furthermore, conducted clinical trials using stem cell therapies for respiratory diseases in the world and particularly in Iran are discussed.

Material content

For data collection, published reports from the literature of the years 2000 to 2017 discussing lung cell therapy were reviewed in the PubMed database, using the keywords "lung diseases", "respiratory", "stem cell" and "cell therapy". Finally, 97 articles were selected and included in the review.

Lung stem cells in lung regeneration

Even after adolescence, mammalian organs and tissues contain some endogenous stem/progenitor cells which cause distribution of a predetermined microenvironment, known as a "niche". A niche consists of the physical environment to which it has become adapted and its role as producer and consumer of life conditions. Through provision of repairing cells, this niche has a key role in maintaining homeostasis and tissue and organ repair. While identification of proliferating cells in the lung under steady state or injury conditions is relatively easy, characterization and classification of putative endogenous lung stem and progenitor epithelial cells into a hierarchy are complicated (8). Most of the evidence in mouse models and, to a lesser extent, in the literature on human lungs describe putative populations of adult endogenous epithelial stem and progenitor cells in airways and alveoli (Figure 1) (9). Pulmonary stem/progenitor cells (including bronchiolar stem cells, bronchioloalveolar stem cells, tracheal and bronchial stem cells, alveolar stem cells and alveolar type II cells) were shown to have a biological function in the repair of injured tissues and in maintaining and recovering

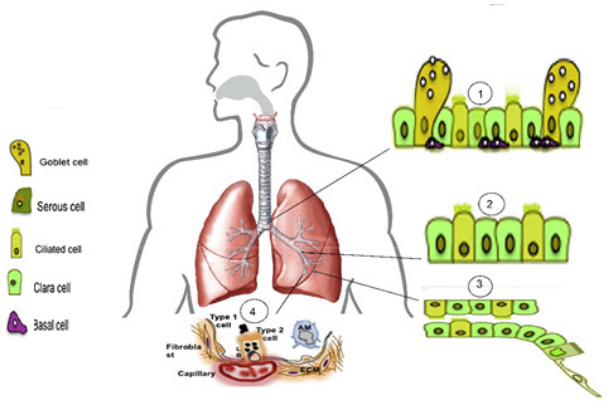

Figure 1. Composition of the lung epithelium. 1: Tracheal Bronchial epithelium, 2: Bronchiolar epithelium 3: Bronchoalveolar duct junction epithelium, 4: Alveoli.

homeostasis. They confer their roles through molecular markers, lineage tracing and clonal analysis (8). Some studies have reported controversial findings, and still there is no consistent agreement regarding identity, the role and function of endogenous epithelial stem or progenitor cells in either human or mouse lung (10,11). Although differentiated epithelial club cells exhibit a low stable state proliferative index, distal mouse airways are able to self-renew and replenish ciliated cells in both the trachea and distal airways during normal homeostasis or injury (12,13). It has become evident that putative airway progenitor cells may be inert in response to less severe injuries and play a negligible role in normal airway epithelial homeostasis (13). As such, endogenous airway progenitor cells are believed to serve as a reserve population, which presents biological function in normal maintenance, as well as when depletion of the facultative progenitor pool occurs. Some findings report that endogenous progenitor cells have a potential role in replenishing or repairing interstitial and vascular components of the lung (14). Furthermore, it was found that lung endogenous stem cells use GFP-labeled in chimera mice. It synergistically causes regeneration of alveoli. Robust preclinical study has revealed that AT2 cells are able to repair the injured alveolar epithelium. However, the ability of pulmonary endogenous stem cells to substitute for injured AT2 cells remains uncertain (8).

Endothelial progenitor cells in lung regeneration

Asahara et al (1997) proposed the idea that immature endothelial progenitor cells (EPCs) are present in adult blood and contribute to postnatal vascular repair or angiogenesis (15). This concept was very interesting because it showed that it may be possible to derive EPCs from peripheral blood as a new treatment in patients suffering from vascular disease. The concept has been discussed in over 4000 publications during the past 15 years (16). Gradually, further evidence revealed the role of EPCs in the pathogenesis of a wide variety of lung diseases, such as pulmonary hypertension, pulmonary fibrosis, asthma, acute lung injury, COPD, BPD, lung cancer and obstructive sleep apnea in children (17). In response to injury, endothelial cells lining the pulmonary microvasculature are believed to be lost into the circulation due to a sloughing off process that releases endothelial micro particles (EMs) and CEC(18). Increased CECs have been observed in vascular circulation diseases (19). This process causes the release of a variety of angiogenic factors, most notably, vascular endothelial growth factor (VEGF), which recruits EPCs to the site, presumably to repair the vascular damage (18). An increasing number of studies show that systemic administration of EPCs can mitigate experimentally-induced lung injuries in preclinical rodent and dog models of pulmonary hypertension, endotoxin-induced acute lung injury and BPD (17). EPCs also appear to home metastatic tumors in lung. Researchers have proposed the idea of EPCs modification to express suicide genes or other therapeutic molecules as a useful approach in cell-based therapy protocols for lung cancer (20,21). EPCs can also preferentially localize in injured areas of lung following systemic administration, and may also have paracrine effects to decrease inflammation (21). Lamiaa

et al showed that pinocembrin significantly enhances the therapeutic properties of endothelial progenitor cells in monocrotaline-induced pulmonary hypertension in rats (22). Most recently, Zhihui et al demonstrated that intratracheal transplantation of EPCs attenuates the development of pulmonary emphysema and lung function disorders. It was postulated that these effects are conferred by decelerating apoptosis, mitigating inflammatory infiltration, enhancing antioxidant activity and preventing proteolytic enzyme activity (23).

Mesenchymal stem cells (MSCs) in lung regeneration

Mesenchymal stem cells (MSCs) are multipotent adult stem cells, followed with significant interest by the medical and scientific community since their initial discovery (24). MSCs have potential application in regenerative medicine, in which they are thought to aid in the repair and regeneration of otherwise physiological damage and incurable diseases, including neurological disorders, immunological diseases, articular cartilage damage and the development of irreversible lung fibrosis (25). MSCs have been found in various sites, such as fetal tissues, adipose tissue and skeletal muscle and lung, but most often are isolated from bone marrow. The isolation and identification of MSCs, however, is complicated due to lack of a distinct surface marker (26). MSCs have several useful functions that make them a potential therapeutic option for regenerative medicine. Among the interesting properties of MSCs are secretion of growth factors and anti-inflammatory cytokines, their ability to "rescue" cells through the transfer of functional mitochondria and their migration of administered cells to the site of injury (27). The possibility of autologous cell transplantation is also suggested, which may help to circumvent immune rejection. These properties, among others, make MSCs a potential therapeutic agent to treat chronic lung diseases with high rates of morbidity and mortality, such as obstructive bronchiolitis (OB), idiopathic pulmonary fibrosis (IPF) and COPD. MSCs have been reported to exhibit immunomodulatory effects by inhibiting the proliferation of T cells7 and by secreting anti-inflammatory cytokines and growth factors. Some findings revealed their ability to migrate to the location of injury when administered, and from there, to differentiate into specific cell types to initiate regeneration (28). There are approximately 90 publications to date about rodent and other preclinical models regarding bacterial lung infection, acute lung injury, bronchiolitis obliterans, asthma, COPD, BPD, pulmonary hypertension, fibrosing pulmonary injury, obstructive sleep apnea, pulmonary ischemia reperfusion injury, sepsis, burns, radiation-induced lung injury, and other critical diseases or autoimmune-related lung injuries, such as pancreatitis, hemorrhagic shock, ventilator-induced lung injury, and silicosis (29,30). It was found that administration of MSCs of either placental or bone marrow origin decreases inflammation and injury in endotoxin or bacterially-injured human lung explants (17). MSCs have become a novel potential therapeutic agent in treating IPF, mainly because of their anti-inflammatory effects, migratory properties and immune privilege (31). MSCs are believed to initiate epithelial tissue regeneration through recruitment of endogenous stem cells to the site of injury and by signaling local stem cell differentiation (28). Of the several treatment options for COPD, as well as those being more intensely studied, none has been found to repair or reverse the damage caused by emphysema. MSCs, however, are a promising therapeutic modality to treat COPD, and are the most extensively researched candidates in COPD clinical trials because of their remarkable capability to migrate to the site of injury and initiate tissue repair (32). Stromal cell-derived factor-1 (SDF-1) is a chemokine with the ability to modulate stem cell recruitment and angiogenesis. It is secreted by MSCs and is considered an essential mediator for MSC reparative effects in experimental bronchopulmonary dysplasia. Table 1 shows the role of this chemokine in repair of the neonatal lung (33). MSCs also exhibit anti-inflammatory and protective abilities through the suppression of inflammatory cytokines and growth factor production, which could potentially assist in repair of lung tissue–destroyed emphysema and the amelioration of inflammation produced by chronic bronchitis (34). With further study, MSCs could potentially alter the progression of COPD (35). Administration of MSCs is believed to inhibit the development of early airway obstruction (AO) in the heterotopic tracheal transplant model of OB (28). The administration of MSCs appears to be a hopeful option for the prevention of BOS in transplant patients. In many patients, transplantation or retransplantation is the only option for end-stage lung disease

Table 1. Factors secreted by mesenchymal stem cell that play essential role in lung repair.

Factors secreted	Role in lung repair	References
NO	Immunosuppression	-37
Interleukin-10	Anti-inflammatory	-38
TGF-β	Immunosuppression	-39
Prostaglandin E2	Anti-inflammatory	-40
IL1RN	Anti-inflammatory, anti-fibrotic	-41
FGF10	Repair, proliferation, and differentiation of epithelial cells.	-14,42
ANGPT1	Reduction of alveolar epithelial permeability and inflammation	-36,37
LL-37	Antimicrobial	-45
KGF	Alveolar fluid transport,	-46
TSG-6	Anti-inflammatory	-47
Lipoxin A4	Regeneration of epithelial cells	-48

(28). Konrad et al demonstrated that intratracheal administration of MSCs positively regulated airway remodeling, attenuated inflammation and improved function, suggesting their ability to maintain and promote tissue homeostasis in experiments in the course of allergic asthma (36). Klein et al (2017) showed that adoptive transfer of MSCs early after irradiation successfully prevented radiation-induced vascular damage and EC loss as a late adverse effect. The remarkable radioprotection properties of vascular wall–derived MSCs are attributed to their tissue-specific action. Currently, clinical trials investigating MSCs' effects on septic shock and acute respiratory distress syndrome (ARDS) are underway in Canada and the US, respectively (Table 1) (17).

Bone marrow–derived stem cells in lung regeneration

Bone marrow is the largest storing pool of stem cells, which are considered the main source of stem/progenitor cells outside the lungs. These potentially repairing cells include EPCs, hematopoietic stem/progenitor cells (HSPCs) and bone marrow–derived mesenchymal cells (BMSCs). During infections, acute injury or a mobilizer administration, they exit the bone marrow pool and under the guidance of chemokines migrate directly to the injured lung tissues. Furthermore, they have a positive role in repairing differentiated cell types (8). Murine studies employing an endotoxin-triggered model of ALI revealed that administration of BM-MSCs soon after injury results in pulmonary hemorrhage, alveolar edema and reduced vascular permeability. A reduction in the levels of pro-inflammatory cytokines (INF-γ, IL-1β, IL-6 and macrophage inflammatory protein 1α) and additional up-regulation of anti-inflammatory cytokines (IL-10) are responses thought to be mediated by both soluble factors and direct cell-cell contact. BM-MSCs prevent T-lymphocyte proliferation and inhibit the differentiation of human monocytes into dendritic cells. This occurs by both direct cell-cell contact and secretion of soluble factors (49,50). There is also evidence that BM-MSCs suppress T cell activity, as shown by their potential to increase survival in transplant recipients with graft-vs-host disease (51). However, the detailed mechanism by which this happens is unclear. Some findings indicate that direct cell-cell contact is needed (52). while other studies imply a role for soluble factors (53). Possibly, each system has a role and the exact mechanism needs further investigation. If, as proposed, BM-MSCs can be mobilized to specific sites in response to an acute injury, and terminate the inflammatory response by modulation of cytokine production and contribute to tissue repair, then they become attractive candidates for treatment of acute inflammatory diseases that result in organ damage, such as ALI/ARDS (54). In the murine model of bronchiolitis obliterans, intraperitoneal administration of BMSCs showed potent effects on cytokine levels and histopathological lesions of lung tissue (55).

Adipose-derived stem cells (ADSCs) in lung regeneration

In regenerative medicine, adult stem cells are the most promising for cell-based therapies. Human adipose tissue is a new and encouraging source for multipotent stem cells. Adipose tissue–derived stem cells (ADSCs) are perfect for use in regenerative therapies (56,57). Their main benefit over mesenchymal stem cells originating from other sources is that they are easily harvested. They exhibit low morbidity in a process conducted through minimally invasive techniques. ADSCs are multipotent and can differentiate into various cell types of the lineages trigger, such as osteocytes, adipocytes, neural cells, vascular endothelial cells, cardiomyocytes, pancreatic cells and hepatocytes (58). Interestingly, ADSCs are believed to have low immunogenicity and immunosuppressive effects. Their production of trophic factors enforces the regenerative and therapeutic results in a wide variety of applications. Taken together, ASDCs' specific properties have made them interesting candidates for clinical applications. As compared with BMSCs, ADSCs were simply harvested from dumped adipose end product via the regular adipose aspiration technique. The total volume of adult bone marrow extracts is 40 ml, while that of adult adipose can easily reach 500 ml (59). In a randomized, placebo-controlled pilot study, ADSCs showed significant protective effects on ALI. Optical imaging analysis further revealed that they enhance subacute airway remodeling, and ameliorate ventilator-induced lung injury in rats (60). The major protective effects were attributed to eNOS and eNOS-derived NO (61). Actually, ADSCs are able to secrete granulocyte colony stimulating factor (G-CSF), hepatocyte growth factor (HGF) and SDF-1 vascular endothelial growth factor (VEGF) when promoting angiogenesis. Besides that, they release laminin and collagen I and III via a paracrine route (62). These factors are believed to have an important role in pulmonary structural repair and functional reconstruction in ALI (8). Lorenzi et al. assessed the effect of adipose tissue–derived mesenchymal stem cell administered either systemically or locally in a murine model. They found remarkable reduction in luminal obliteration when a second dose of ASC was administered systemically in a heterotopic tracheal transplantation model in mice. These results suggest that ASC can be used to prevent obliterative bronchiolitis after lung transplantation (63).

Embryonic stem cells in lung regeneration

Recently, the use of differentiating cultures of embryonic stem cells, as a promising alternative source of committed lung progenitor or stem cells, has increased. Some reports have shown explanatory conditions that contribute to the differentiation of mouse embryonic stem cells into heterogeneous populations. This process involves subsets of cells capable of expressing lung epithelial cell–specific markers, such as surfactant protein C (SP-C) and Clara cell secretory protein (CCSP) (64,65). Further manipulation of culture conditions used for the directed differentiation of ES cells may have potential to increase the efficiency of the condition in which lung progenitor cells are produced *in vitro* (66). Human embryonic stem cell–derived progenitor cells could ameliorate sepsis-induced inflammatory lung injury (67). Meanwhile, researchers could obtain functional airway epithelium from human embryonic stem cells through

an extensive generation measure. However, owing to ethical bottlenecks and legal disputes, such embryonic stem cells should not be recommended as perfect seed cells in the repair and regeneration of injured lungs (8).

Placenta-derived stem cells in lung regeneration

Placenta-derived stem cells (p-SCs) rank between mesenchymal and embryonic stem cells. They share characteristics with both, such as differentiation to all embryonic germ layers and non-carcinogenic status. Moreover, placental membranes are considered medical waste and their use is not ethically limited. p-SCs, including amniotic epithelial and mesenchymal stromal cells, chorionic mesenchymal stromal and trophoblastic cells and HSCs (68). Placenta-derived stem cells have been evaluated for use in the treatment of pulmonary diseases in animal models. Intratracheal or intraperitoneal administration of placenta-derived stem cells (PDSCs) in a bleomycin-induced model of pulmonary fibrosis attenuates the amount of fibrosis, compared to controls. Decreased neutrophil infiltration and attenuated expression of pro-inflammatory cytokines (69). The administration of amniotic fluid stem cells (AFSCs) significantly decreases hyperoxia-induced pulmonary inflammation, as reflected by significant decreases in lung wet/dry ratio, neutrophil counts, the level of apoptosis, declining levels of inflammatory cytokine (IL-1β, IL-6, and TNF-α) and early stages of lung fibrosis. Moreover, grafting EGFP-expressing AFSCs into a peripheral lung epithelial cell lineage is conducted using DAPI stain and fluorescence microscopy (8). Umbilical cord blood–derived human CD34+ progenitor cells have been found to prevent LPS-induced inflammatory lung injury (70). Likewise, MSCs from umbilical cord blood were found beneficial in an ARDS patient when administered intratracheally (71).

Lung bioengineering

Many devastating lung diseases, such as IPF, cystic fibrosis and COPD, have no cure, causing notable mortality and morbidity. Furthermore, the prevalence of lung diseases, particularly COPD, is increasing. It is predicted that COPD will be the third leading cause of death worldwide by 2020 (72). Only limited numbers of suitable donor lungs and lung transplants are available, a circumstance further complicated by noticeable graft failure and complications of immunosuppressive medications. An alternative to classic organ replacement is desperately needed. Engineering bioartificial organs, using either natural or synthetic scaffolds, are an inspiring option for production of functional pulmonary tissue for human clinical utilization (73,74). Natural organ scaffolds can be produced using native tissues subjected to decellularization. Acellular scaffolds hold the native organ ultrastructure and can be seeded with autologous cells to regenerate functional tissues. Several decellularization strategies have been employed for the lung; however, there is no agreement on the optimal approach (Figure 1) (75). Several cell types have been examined as possible candidates for efficient recellularization of acellular lung scaffolds (76). Candidate cells that might be best suited are those which can be separated easily, expanded *in vitro*, seeded onto decellularized matrices and easily differentiated into pulmonary lineage cells with high survival to functional maturity. Whole lung cell suspensions, induced pluripotent stem cells (iPS), embryonic and adult stem cells and endogenous progenitor cells have been examined for their applicability to repopulate acellular lung matrices. Due to its potential to reduce post-transplant immunosuppression, lung recellularization is conducted using patient-derived autologous cells (75). The challenges in developing complex 3D functional lung tissues *ex vivo* will be in recapitulating the normal dynamic integrated 3D network of cells in the appropriate environment and architecture. Other approaches such as human capillary endothelial cells and human epithelial cells covered onto porous polydimethylsiloxane chips can simulate alveolar architecture and can be employed to investigate pathophysiologic processes and also high-throughput drug screening (77). However, it is still practical to produce part of the upper or lower airway or the alveolar tissue. In fact, important progress has recently been made using decellularized or synthetic scaffolds to generate tracheal cartilage as well as tendon tissue in the diaphragm for clinical utilization (78). MSC-derived chondrocytes and epithelial cells are inserted into the decellularized donor trachea, returning trachea function to the recipient (79). Currently, the production of alveolar tissues and those of the lower airway is more challenging and limited to animal studies (35). Most recently, Nichols et al have produced bioengineered human lungs for the first time, showing the ability to repopulate the lungs (Figure 2) (80).

Clinical trials of cell-based therapies for lung diseases

Stem cell therapy has been widely debated and introduced as a new therapeutic approach for degenerative diseases. For clinical use, stem cells from the sources described above are extracted, isolated, and cultured in a bioreactor to be injected into the patient (Figure 3).

Preclinical literature strongly advocates MSCs in acute lung injury or inflammatory critical illnesses, as well as in more chronic inflammatory and immune-mediated conditions such as bronchiolitis obliterans, Broncho pulmonary dysplasia and asthma (Figure 4) (17). In 2013, a phase I clinical trial of cell therapy was conducted in patients with advanced COPD. The results showed that autologous cell therapy is a safe method in COPD patients with no side effects. Improvement of

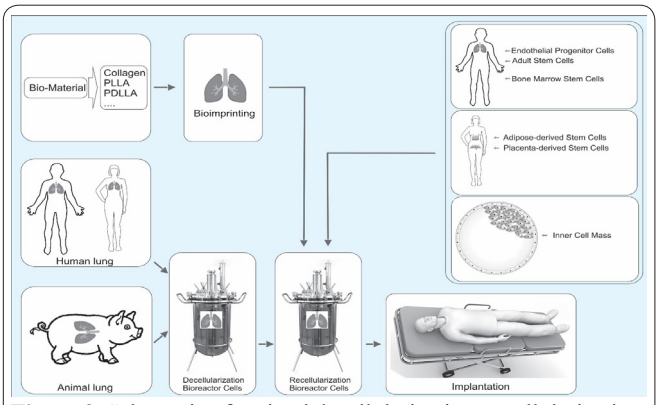

Figure 2. Schematic of optimal decellularization, recellularization, and implantation in lung tissue engineering.

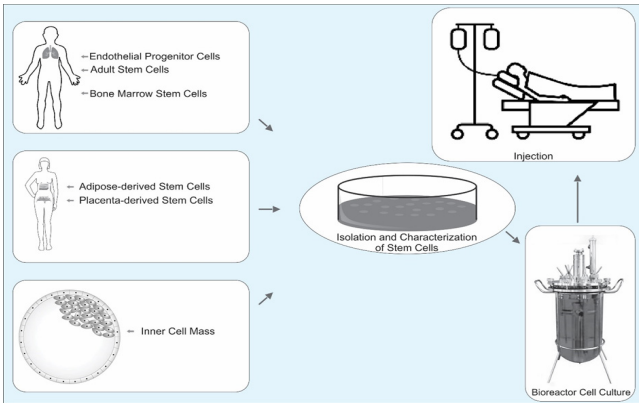

Figure 3. Schematic of optimal decellularization, recellularization, and implantation in lung tissue engineering.

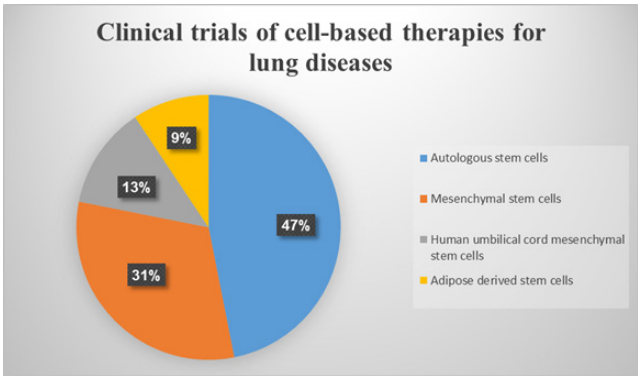

Figure 4. Autologous stem cells are most commonly used for treatment of clinical pulmonary diseases. They consist of cells originated from bone marrow and Peripheral blood of under treatment cases. The mesenchymal cells used in these clinical studies often include allogeneic cells derived from bone marrow. (ClinicalTrials.gov).

laboratory parameters (spirometry) and deceleration in the process of pathological degeneration were observed. Patients reported improvements in their clinical symptoms and quality of life (81). ARDS is a common problem in intensive care units. Even though the results of a comprehensive study showed that ARDS mortality rate still stands as high as 40%. Current supportive treatments are conservative fluid strategy and lung-protective ventilation (82). Recent experimental studies suggested that cell-based therapies, particularly mesenchymal stem/stromal cells (MSCs), pluripotent or embryonic stem cells and endothelial progenitor cells all offer notable promise for ARDS (83). Multiple groups have shown the useful effects of systemic administration of B-MSC to control ARDS, mainly by their anti-inflammatory properties (84). IPF is an interstitial lung disease identified by deposition of collagen, resulting in scarring of the lung. Daniel C et al (2014) showed that intravenous MSC administration is feasible and has a good short-term safety profile in patients with moderately severe IPF (85). Marilyn et al examined the intravenous administration of allogeneic human mesenchymal stem cells (hMSC) in patients with idiopathic pulmonary fibrosis. Data from this phase I trial supported the safety of a single infusion of hMSC in patients with mild-to-moderate IPF (86). Recently, Zhang et al showed that intravenous infusion of human umbilical cord-derived mesenchymal stem cell (HUC-MSC) seems to be beneficial to patients with IPF and may be used as an additional therapeutic choice (87). A phase II clinical trial was conducted to investigate the potential efficacy of MSC administration for the treatment of airway diseases. It was shown that after 2 years of follow-up post-MSC administration, no improvement was observed in the patients with moderate symptoms. However, the overall purpose of the project was to determine the efficacy and safety of MSCs (88). In the studies by Jeong Chan et al, the safety of human Adipose Tissue-Derived Mesenchymal Stem Cells (hATDMSC) for the treatment of toxicity and tumorigenesis was investigated in animals and human subjects (89). Tzouvelekis et al (2013) examined the possibility to use mesenchymal stem cells from adipose tissue for the treatment of idiopathic pulmonary fibrosis. In their study, preliminary results showed that no allergic reactions, infections, acute exacerbations or ectopic tissue formations has been attributed to the stem cells. In addition, based on 6 months of follow-up data, no significant differences were observed in the 6 minute walk test (6MWT) and forced vital capacity (90). Liang et al. in 2012 showed that intravenous injection of BMSCs facilitates more rapid repair in patients with lung diseases caused by various chemical warfare agents and biological toxins, without side effects. Pulmonary function tests and spirometric measurements were analyzed to evaluate their potential role in the treatment of patients (91). Numerous clinical trials using MSCs to prevent and treat graft-versus-host disease (GVHD) have been conducted worldwide (92); moreover, MSCs are thought to suppress acute and chronic GVHD without damaging the graft-versus-leukemia effects, thus representing a novel treatment for GVHD (89). Comella et al investigated the early and delayed safety of stromal vascular fraction (SVF) infusion in an initial phase I trial. SVF holds all cellular components of fat, excluding adipocytes. They found SVF infusion to be a safe treatment for the first time in patients with serious pulmonary disease (93). Talita et al (2012) conducted a phase I clinical trial in patients suffering from advanced COPD. The results revealed that autologous cell therapy is a safe method and has no negative effects (81). The combination of the intrabronchial MSC administration and bronchoscopic lung volume reduction (BLVR) through endobronchial valve placement appears seem to be safe and may reduce systemic inflammation in severe COPD patients(94). Until now, 15 studies were registered by the ClinicalTrials.gov, which employed different protocols of stem cell therapy for COPD (Table 2). Most of these included bone marrow–derived stem cells and adipose-derived stem cells. Published results of three trials indicated that administration of BMMCs or MSCs in the repair of damaged lung tissue is safe and may improve patients' condition and quality of life. However, more evidence is needed to confirm the efficacy of this treatment (95). A large number of clinical trials for the therapeutic application of stem cells in lung diseases are mentioned on the ClinicalTrials.gov website, which reflects growing efforts for accurate examination of these cells regarding their use for treatment of pulmonary diseases and the efficacy and safety of these herapeutic cells in lung injuries as well (Figure 4) (17).

In Iran, the first clinical trial in association with stem cell therapy in lung disease was published by Ghanei

Table 2. Studies were registered by the ClinicalTrials.gov, which employed different protocols of stem cell therapy for COPD.

Responsible Party	Cell Type	Delivery Route
Phuc Van Pham, University of Science Ho Chi Minh City. Vietnam (2016)	ADSCs	IV
Melissa Rubio, PhD, APRN, Lung Institute. United States (2017)	Autologous Stem Cell (bone marrow)	IV
João Tadeu Ribeiro Paes, UPECLIN HC FM Botucatu Unesp. Brazil (2010)	Autologous Stem Cell (bone marrow)	IV
João Tadeu Ribeiro Paes, UPECLIN HC FM Botucatu Unesp. Brazil (2015)	Autologous Stem Cell (BMMC)	IV
Melissa Rubio, PhD, APRN, Lung Institute. United States (2017)	Autologous Stem Cell(peripheral blood)	IV
Arkansas Heart Hospital. United States (2017)	ADSC	IV
Melissa Rubio, PhD, APRN, Lung Institute. United States (2017)	Autologous Stem Cell(peripheral blood or from bone marrow)	IV
Mesoblast International Sàrl. United States (2008)	ex Vivo Cultured Adult Human Mesenchymal Stem Cells	IV
StemGenex. United States (2015)	Autologous Adipose Stromal Vascular Fraction	IV
ZiLi Meng, Huai'an No.1 People's Hospital. China (2017)	autologous bronchial basal cell transplantation	Bronchoscopy (injected directly into the lesion site)
Kimera Society Inc United States (2014)	ADSC	IV
Elliot Lander, Cell Surgical Network Inc. United States (2013)	autologous adipose derived stromal vascular fraction	(Intra-venous, intra-articular, and soft tissue injection delivery)

et al (2015), entitled, "Adipose-Derived Mesenchymal Stem Cells for Treatment of Airway Injuries in a Patient after Long-Term Exposure to Sulfur Mustard". The purpose of this study was to evaluate the safety and potential efficacy of systemic MSC administration on chronic lung injuries induced by SM exposure. No serious adverse events or infusion toxicities were observed after MSC administration. Although no significant difference was observed in pulmonary function tests, they found significant improvement in the 6MWT, as well as the Borg Scale Dyspnea Assessment (BSDA), Assessment Test and St. Georges Respiratory Questionnaire (SGRQ) scores after each injection (96). In sulfur mustard–exposed patients, the efficacy of systemic administration of mesenchymal stem cells on the expression of inflammation related and oxidative stress genes. The results showed that mesenchymal stem cells reduced inflammation and oxidative stress in these patients (97). In addition, two studies have been recorded on the ClinicalTrials.gov website, entitled "Mesenchymal Stem Cells Therapy for Treatment of Airway Remodeling in Mustard Patients" and "Safety Study of Endobronchial Transplantation of Autologous Mesenchymal Stem Cells (MSCs) in Emphysema Patients" that the running.

Conclusion

Our study demonstrates that cell transplantation for respiratory diseases and transplanted cells can contribute to lung repair and construct of lung. However, cell therapy for tissue engineering and treatment of lung diseases still is at its very beginning, and little is known about the effects of administering any type of cell therapy to patients with lung diseases. Therefore, more study, especially at the clinical trial level is needed. Due to the potential for harm, the lack of any proven advantage, and the high costs of many of these programs, participation in any illegal or unapproved stem cell administrations is inadvisable, unless independent credible, authentic, effective and objective sources of information are available to prove the information and claims being made. To summarize, in the regeneration medicine field and especially in cell therapy, lung diseases will be candidates for gene modification, immune cell therapy, stem cell therapy and tissue engineering. However, further studies investigating the role of transplanted stem cells will provide improved insight into the mechanisms of lung repair and development after dysfunction and may also provide novel and more efficient therapeutic strategies for medical application.

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