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Cell Therapy Approaches for Lung Diseases: Current Status

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Summary and recent advances

Recent findings suggest that embryonic stem cells and stem cells derived from adult tissues, including bone marrow and umbilical cord blood, could be utilized in repair and regeneration of injured or diseased lungs. This is an exciting and rapidly moving field that holds promise as a therapeutic approach for variety of lung diseases. Although initial emphasis was on engraftment of stem cells in lung, more, recent studies demonstrate that mesenchymal stem cells (MSCs) can modulate local inflammatory and immune responses in mouse lung disease models including acute lung injury and pulmonary fibrosis. Further, based on initial reports of safety and efficacy following allogeneic administration of MSCs to patients with Crohn’s disease or with graft-versus-host disease, a recent trial has been initiated to study the effect of MSCs in patients with chronic obstructive pulmonary disease. Notably, several recent clinical trials have demonstrated potential benefit of autologous stem cell administration in patient with pulmonary hypertension. In this review, we will describe recent advances in cell therapy with the focus on MSCs and their potential roles in lung development and repair.

Keywords
Mesenchymal Stem Cells; Lung; Cell Therapy; Tissue Bioengineering

Introduction

Over the past decade, a number of reports have suggested that both embryonic and adult tissue-derived stem cells can participate in the regeneration and repair of diseased adult organs including the lungs (1**). These findings present an exciting potential therapeutic
approach for a variety of lung diseases particularly as investigations of stem cells and cell therapies in lung biology and diseases have continued to expand.

However, the field has undergone some changes in emphasis. While both embryonic and adult stem cells can be induced in vitro to express phenotypic markers of airway and/or alveolar epithelial cells, engraftment of airway or alveolar epithelium by stem or progenitor cells following systemic administration is rare and of unclear physiologic or therapeutic significance (1–3). Structural repair or replacement of injured lung epithelial cells by administering exogenous stem cells is now felt to be less likely. In contrast, engraftment of pulmonary vascular endothelium by autologous bone marrow-derived endothelial progenitor cells and stimulation of neoangiogenesis has been the basis of recent clinical trials of EPCs for pulmonary hypertension (4–7). These initial trials have suggested improvement in both clinical measures of pulmonary hypertension as well as in cardiopulmonary physiologic variables in both adult and pediatric patients. Although, only short term assessments have been made and the number of patients studied relatively small, these are encouraging studies that are being followed up with larger longer term studies. Importantly, no significant adverse effects have been reported.

More recently, focus has been on exploration of 3-dimensional culture systems and bioengineering approaches to generate functional lung tissue ex vivo and in vivo (8*, 9*). Further, MSCs have been demonstrated to have an immunomodulatory effect as demonstrated by suppression of inflammation in murine models of lung injury (10, 11). These studies have been the basis of a recently initiated trial of allogeneic MSC administration in patients with chronic obstructive pulmonary disease.

**Structural Engraftment and Functional Effects of Exogenous Stem or Progenitor Cells**

Over the past decade, a number of publications have suggested that a variety of bone marrow-derived cells including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), multipotent adult progenitor cells (MAPC), and other populations could structurally engraft as mature differentiated airway and alveolar epithelial cells (2*, 3, 12). However, this is now felt to be a rare occurrence which raises the question whether functional epithelial engraftment does in fact occur (1**, 13). Nonetheless, recent studies have confirmed that engraftment of donor-derived airway and/or alveolar epithelium, although rare, can occur following perturbation of airway or alveolar epithelium in lung injury models. Engraftment by MSCs of bone marrow or cord blood origin (2*), side population cells (14*), plastic adherent marrow stromal cells (3, 15) or full marrow transplantation following a myeloablative regimen (16, 17) in lung tissues usually occurs following lung injury. Further, recent studies demonstrate that chronic or progressive lung injury may result in more substantial engraftment of type 2 alveolar epithelial cells and of interstitial and pulmonary vascular cells with donor-derived cells in mouse or rat models (16, 18).

One major focus is how engraftment of airway or alveolar epithelium with exogenous cells can be improved. There are many variables still left to be explored that may increase
epithelial, interstitial, or pulmonary vascular engraftment with circulating or donor-derived cells. These include (i) route of cell administration i.e. intratracheal (19) vs systemic administration (19). (ii) the type of cells used i.e. CD45+/CXCR4+/cytokeratin+ cells (20), (iii) other sources of stem or progenitor cells i.e. adipose tissues, placenta. Further, the mechanisms of airway epithelial cell engraftment by exogenously administered stem cells are not well elucidated. Both in vitro and in vivo studies suggest that fusion might play a role (21*, 22). However, other mechanisms might be involved. Further, the mechanisms by which stem or progenitor cells might be induced to acquire the phenotype of lung epithelial cells remain poorly understood. In vitro studies continue to demonstrate that soluble factors released from lung epithelial cells or from injured lung homogenates can induce expression of lung epithelial markers in several types of marrow-derived cells, possibly through activation of β-catenin signaling pathways (23). One novel mechanism of inducing phenotypic change might involve release of membrane-derived microvesicles, a recently appreciated means of inter-cellular communication that involves horizontal transfer of mRNA and proteins between cells (24*, 25).

Importantly, mechanisms by which circulating or systemically administered stem or progenitor cells might be recruited to lung remain poorly understood. Following systemic administration, many cells initially localize in lung and injury results in increased localization and/or retention of marrow-derived cells in lung (26–28). The timing of cell administration after lung injury can also influence recruitment and phenotypic conversion of donor-derived cells. Systemic administration of MSCs 4 hours after lung irradiation resulted in apparent engraftment of cells as epithelial and vascular endothelial cell (28) while administration of cells at the later time points resulted in MSC engraftment as interstitial cells and participation in development of fibrosis (28, 29). Recipient immune responses also play significant yet poorly characterized roles in retention of cells in lung (30). The range and identity of chemotactic soluble mediators released by injured lung cells and the role of up-regulation of adhesion molecules with which circulating cells might interact remains poorly understood (1**, 31). As with engraftment, a number of factors including age of donor or recipient, type of cell administered, route of administration, etc all might affect recruitment to lung.

**Lung Tissue Bioengineering**

One growing area of investigation is that utilizing three-dimensional matrices or other artificial scaffolding for growth of functional lung tissue from stem cells *ex vivo* and *in vivo*. These approaches have been increasingly successfully utilized in regeneration of other tissues including skin, vasculature, cartilage, and bone. Notably, MSCs isolated from amniotic fluid, umbilical cord blood, adipose tissues or bone marrow can be seeded on biodegradable polyglycolic acid or other biosynthetic scaffolds and generate tracheal cartilage for use in repair of congenital tracheal defects and also tendon tissue for use in congenital diaphragmatic defects (32, 33). Studies in animal models and a recent clinical investigation suggest safety and efficacy and clinical trials in neonates with congenital tracheal or diaphragmatic defects are planned (32–34). Most recently these approaches have resulted in successful clinical use of a bioengineered trachea (35).
Given the complex three-dimensional architecture of the lung, engineering functional lung parenchyma ex vivo is a daunting task. However, both in vitro and in vivo studies utilizing mixed fetal lung cells cultured in a three dimensional glycosaminoglycan (GAG) or other type of scaffolds resulted in formation of alveolar-like structures in the scaffold (9*, 36). Notably, stimulation of murine fetal lung cells in polymer scaffolds with different isoforms of fibroblast growth factor resulted in different patterns of development demonstrating the power of three-dimensional culture systems to evaluate lung development and repair (37). In vivo, a recent study demonstrated that fetal rat lung cells cultured in a biodegradable gelatin sponge, and subsequently injected into normal rat lungs, induced formation of branching, sacculated epithelial structures reminiscent of lung parenchymal architecture (36). Mixed fetal murine epithelial cells admixed with Matrigel and injected subcutaneously into the abdominal wall of adult mice demonstrated cells that expressed pro-surfactant protein C after 1 week (38). These studies demonstrate the potential of in vivo lung tissue generation utilizing mixed populations of fetal lung cells. However, this is not a practical approach and lung tissue engineering with stem or progenitor cells is a more feasible potential therapeutic option. Further, there are few studies as yet evaluating whether stem or progenitor cells isolated from adult bone marrow, cord blood, or other sources can also comparably form airway or alveolar-like structures when cultivated in a three-dimensional matrix or other scaffolding material and whether stem or progenitor cells cultured in such fashion can be utilized for functional lung regeneration in vivo. A population of cells described as adult lung somatic progenitor cells isolated from adult sheep lungs cultured in synthetic polymer constructs resulted in expression of airway and alveolar epithelial markers by the cells (39). Structures resembling lung airways and parenchyma developed when impregnated constructs were implanted subcutaneously in nude mice or inserted into the wound cavity following wedge lung resection in sheep. Adipose-derived MSCs, cultured ex vivo in sheets of polyglycolic acid and then applied to wound edges following lung volume reduction surgery in rats, accelerated alveolar and vascular regeneration (40). Further studies to understand the role of three-dimensional scaffold on stem cell differentiation and cell fate will be important.

**Immunomodulatory Property of MSCs**

The ability to structurally engraft in adult lung may not be the only potentially relevant property of exogenously administered stem or progenitor cells. For example, MSCs have been shown to differentiate into a wide range of cell types and to produce a number of growth factors and cytokines that are important for tissue repair and remodelling. Further, MSCs express intermediate to low levels of HLA class I, low levels of HLA class II, and low levels of co-stimulatory molecules allowing the MSCs to escape alloreactive recognition (41**). Moreover, MSCs suppress allogeneic T-cell proliferation and do not elicit an immune response after transplantation in immunocompetent recipients (42). These properties result in modulation of the immune response by MSCs and have been the basis for clinical trials of allogeneic MSC administration to patients with several inflammatory and immune-mediated diseases including Crohn’s and graft-versus-host disease (43–45). The mechanisms of MSCs actions on inflammatory and immune cells are not well

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understood but likely involve both secretions of soluble mediators as well as cell-cell contact.

In mouse models of lung disease, systemic administration of MSCs immediately after intratracheal bleomycin administration decreased subsequent lung collagen accumulation, fibrosis, and levels of matrix metalloproteinases (1**). Only minimal putative engraftment of the MSCs as lung epithelial cells was observed and secretion of IL-1 receptor antagonist by the MSCs has been hypothesized to account for at least some of these effects (46*). Intratracheal administration of MSCs 4 hrs after intratracheal endotoxin administration decreased mortality, tissue inflammation, and concentration of pro-inflammatory mediators, such as TNFα and MIP-1β, in bronchoalveolar lavage fluid compared to endotoxin-only treated mice (19). Systemic MSCs administration also decreased lung inflammation following endotoxin administration in mice and co-culture of MSC with lung cells obtained from LPS-treated mice resulted in decreased pro-inflammatory cytokine release from the lung cells (19, 47). More recent data suggests that release of angiopoietin-1 by the MSCs and stabilization of alveolar-capillary permeability and endothelial fluid leak in the setting of endotoxin effects on the alveolar capillary barrier may be a relevant mechanism (48, 49). These results suggest potent actions of MSCs in lung but there is still much to be learned.

Preclinical and Clinical Uses of MSCs

Currently, there are a total of 67 clinical trials on the use of both autologous and allogeneic MSCs for variety of diseases including Crohn’s disease, multiple sclerosis, end-stage liver diseases, as a prevention for graft-versus-host-disease following transplantation, for patients with ventricular dysfunction, refractory systemic lupus erythematosus, diabetes mellitus, and most recently for chronic obstructive pulmonary disease (COPD) (50**). A phase I trial of a commercial MSC preparation, Prochymal™ (Osiris Therapeutics Inc, Columbia MD), has been completed in steroid resistant GVHD in 46 patients. There were no drug related serious adverse events (SAEs) and over the two year study there was a reduction in observed mortality from 45 to 22% (51). Based on this data, a phase II trial was initiated in 32 patients with acute GVHD, which has shown a 90% response rate (partial and complete responses) (44). A phase 3 clinical trial is currently underway (52). A comparable phase II open label trial utilizing Prochymal™ has recently been completed for patients with moderate to severe Crohn’s disease who had previously failed treatment with steroids, infliximab and other immunosuppressive agents. Every patient evaluated reported an improvement of symptoms as indicated by a reduction of Crohn’s Disease Activity Index (CDAI) by day 28 after the infusion with an average improvement of CDAI of 62 points by day 7 (52). One-third of the patients achieved clinical remission of the disease based on reported Inflammatory Bowel Disease Questionnaire (IBDQ) scores of at least 170 points (52). Further, no significant SAE’s were observed (52). Currently, Prochymal™ is approved by FDA to advance into a phase III double-blind placebo-controlled trial for the treatment of Crohn’s Disease (43). Future studies are being designed to determine optimal dose, dosing frequency, and durability of response, suitability of biomarkers as surrogate outcome measures, and effects on mucosal healing, as well as long-term safety.
Most recently, a multicenter double-blinded placebo control Phase II trial of allogeneic MSC infusions utilizing PROCHYMAL™ for patients with moderate-severe chronic obstructive pulmonary disease (COPD) (FEV1/FVC <0.70, 30% ≤ FEV1 ≤ 70%) was initiated in May 2008 (45). This trial parallels comparable trials utilizing allogeneic MSC infusion for graft-versus-host disease and for Crohn’s disease. It is based on the hypothesis that anti-inflammatory actions of MSCs will decrease pulmonary and perhaps systemic inflammation associated with COPD and improve lung function, dyspnea, and quality of life. Engraftment and/or regeneration of destroyed lung tissue is not hypothesized to be a significant potential mechanism of MSC action in this trial. Primary efficacy endpoint assessments include pulmonary function testing, and health related quality of life assessments. Safety assessments further include monitoring of blood counts, electrolytes, liver function tests, urinalyses, physician global assessments, time to hospitalization and hospitalization rates, time to COPD exacerbation and COPD exacerbation rates, use of rescue inhalers, and assessment of pulmonary hypertension by echocardiography. Safety endpoints also include monitoring of adverse events, toxicity, and overall survival and survival time.

**Conclusion**

A continuing accumulation of data in both animal models and in clinical trials suggests that cell based therapies may be potential therapeutic strategies for lung repair and remodeling after injury. In parallel, further understanding of the role of endogenous lung progenitor cells will provide further insight into mechanisms of lung development and repair after injury and may also provide novel therapeutic strategies. It is hoped that new research programs will provide further understanding of mechanisms of repair of lung injury and further provide a sound scientific basis for therapeutic use of stem and cell therapies in lung diseases.

**References**

* Of special interest

** Of outstanding interest

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