

# Tissue regeneration as next-generation therapy for COPD – potential applications

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**Abstract:** COPD is a major cause of chronic morbidity and mortality worldwide, and there is a need to develop more effective therapeutic strategies to replace specialized treatment such as lung transplantation. Recent studies suggest that recognition of apoptotic lung epithelial or endothelial cells may result in growth factors to stimulate cell replacement, and defects in these processes may contribute to the pathogenesis of COPD. Furthermore, recent animal and human studies have revealed that tissue-specific stem cells and bone marrow-derived cells contribute to lung tissue regeneration and protection, and thus administration of exogenous stem/progenitor cells or humoral factors responsible for activation of endogenous stem/progenitor cells may be a potent next-generation therapy for COPD.

**Keywords:** COPD, regenerative medicine, cell therapy, stem cell, bone marrow, growth factor

## Introduction

COPD is a major cause of chronic morbidity and mortality worldwide, and the World Health Report 2004 from WHO estimated 2.75 million deaths by COPD in 2002 (WHO 2004). Pulmonary emphysema, a major component of the morbidity and mortality in COPD, is characterized by permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls (Wright and Churg 2006). Only cigarette smoking cessation and long-term oxygen therapy improve survival in COPD (Celli and MacNee 2004; Anthonisen et al 2005), and patients with severe COPD require invasive treatment such as lung transplantation. Therefore, there is a need to develop less invasive, more effective therapeutic strategies for COPD.

It has been demonstrated that all-trans-retinoic acid (ATRA), a metabolite of retinol associated with the process of alveolar septation (Ong and Chytil 1976), can restore the normal lung structure in rats with emphysema (Massaro and Massaro 1997), suggesting the possibility of tissue regeneration in COPD. Since then, a number of studies demonstrating lung repair by means of stem/progenitor cells or humoral factors have been reported in animal models. This article reviews recent advances in regenerative medicine in COPD and its potential application.

## Lung repair mechanisms in COPD

### Apoptotic clearance in COPD

It has been reported that cell death in epithelial and endothelial alveolar cells are increased in patients with pulmonary emphysema (Kasahara et al 2001; Yokohori et al 2004). In general, apoptotic cells are removed from tissues, followed by cell replacement to maintain homeostasis. Recognition of apoptotic cells initiates production of growth/maintenance factors for both epithelial and endothelial cells, and stimulates endothelial angiogenic responses (Weihua et al 2005). Thus, signals from apoptotic cell recognition may contribute to stimulation, release, and/or attraction of progenitor cells for tissue regeneration (Henson et al 2006). Therefore, the presence

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of apoptotic cells in COPD may imply defects in these clearance mechanisms (Henson et al 2006). In fact, there is increasing evidence that apoptotic clearance mechanisms are less effective in COPD lungs and that macrophages from such lungs show a defect in recognizing and ingesting such targets (Hodge et al 2003).

### Tissue-specific stem cells in the lung

In the lung, epithelial stem cells include type II pneumocyte in the alveolus and the Clara cell in the bronchiole (Mason et al 1997; Majka et al 2005). Reddy et al demonstrated that E-cadherin-negative subpopulation of type II cells were proliferative and exhibited high levels of telomerase activity (Reddy et al 2004). Kim et al isolated a pulmonary stem cell population at the bronchioalveolar duct junction, and it may maintain alveolar type II cells of the distal lung and Clara cells in the bronchiole (Kim et al 2005). Hong et al also demonstrated that tracheal basal cells represent a multipotent progenitor cell type for renewal of the injured tracheal epithelium induced by naphthalene (Hong et al 2004). On the other hand, side population (SP) cells, which are more primitive adult stem cells and found in various tissues, have been recently identified in the lung tissue (Summer et al 2003; Summer et al 2004). SP cells comprise 0.03%–0.07% of mouse lung cells and are sca-1-positive, lineage-negative, and heterogeneous at CD45. In addition, Giangreco et al indicated that sca-1-positive, CD45-negative SP cells from mouse lung had a molecular phenotype similar to neuroepithelial body-associated variant Clara cells (Giangreco et al 2004), which are label-retaining cells with multipotency (Hong et al 2001).

### Bone marrow-derived stem/progenitor cells

It has been demonstrated that circulating endothelial progenitor cells (EPC) are decreased in COPD patients and could be correlated with disease severity (Fadini et al 2006; Palange et al 2006). These results raise the possibility that bone marrow cells may be involved in lung regeneration or protection. EPC have been mobilized into the circulation in mice with lipopolysaccharide (LPS)-induced lung injury (Yamada et al 2004) and in patients with bacterial pneumonia (Yamada et al 2005), and large numbers of bone marrow-derived progenitor cells appeared in active fibrotic lesions in the lung of bleomycin-treated mice (Hashimoto et al 2004). However, whether EPC plays a role in the loss of capillaries, in the remodeling of the vascular bed or in the thickening of the small airway wall remains to

be elucidated (Randell 2006). In human lung allografts, recipient-derived cells were integrated into pulmonary epithelium, and epithelial chimerism occurred in bronchi, type II pneumocytes and seromucous glands surrounding larger bronchi (Kleeberger et al 2003). Suratt et al examined human lung specimens from a retrospective cohort of female allogeneic hematopoietic stem cell transplant recipients who received stem cells from male donors, and found significant rates of epithelial (3%–8%) and endothelial (38%–42%) chimerism (Suratt et al 2003).

### Potential strategies for tissue regeneration in COPD

#### Administration of humoral factors responsible for lung regeneration

Because recognition of apoptotic cells by macrophages in COPD is related to the production of hepatocyte growth factor (HGF) by these macrophages, administration of HGF might compensate for the defects in apoptotic clearance in COPD macrophages (Morimoto et al 2001). It has been demonstrated that HGF induces angiogenesis in elastase-injured lung injury through mobilizing endothelial progenitor cells (Ishizawa et al 2004b). In addition, induction of HGF expression by a gene-transfection method resulted in improved pulmonary function via inhibition of alveolar cell apoptosis, enhancement of alveolar regeneration, and promotion of angiogenesis in rats with elastase-induced emphysema (Shigemura et al 2005).

Fibroblast growth factor-2 (FGF-2), an angiogenic factor indispensable for lung development and branching morphogenesis, has been shown to induce an increase in pulmonary blood flow in the damaged lung and a volume reduction in the emphysematous lung, and lead to recovery of pulmonary function in dogs with emphysema (Morino et al 2005); however, FGF-2 could not achieve parenchymal regeneration and alveolar septation.

Vascular endothelial growth factor (VEGF) is a potent mediator of angiogenesis and vascular permeability (Ribatti 2005), and may be involved in many processes in COPD including pulmonary vascular remodeling and endothelial and epithelial cell apoptosis (Papaioannou et al 2006). The complexity of the roles of VEGF and its receptors suggests that strategies specifically targeting VEGF in COPD would have unpredictable and possibly deleterious effects on some of the different processes (Kanazawa 2007).

ATRA (Massaro and Massaro 1997; Belloni et al 2000) or granulocyte-colony-stimulating factor (G-CSF) promoted

lung regeneration and increased bone marrow-derived cell numbers in alveoli in mice with elastase-induced emphysema (Ishizawa et al 2004a). However, the effect of ATRA in the treatment of pulmonary emphysema in animals and humans remains controversial (Massaro and Massaro 2000; Mao et al 2002; Fujita et al 2004; March et al 2004; Roth et al 2006). The Feasibility of Retinoids for the Treatment of Emphysema (FORTE) study was established by the National Institutes of Health/National Heart, Lung, and Blood Institute as an initial step in evaluating the clinical feasibility of retinoid-based therapy (Roth et al 2006). No definitive clinical benefit related to the administration of retinoids was observed. However, time- and dose-dependent changes in  $D_{LCO}$ , CT density mask score, and health-related QOL were observed in subjects treated with ATRA, suggesting the possibility of exposure-related biological activity that warrants further investigation.

We have demonstrated that adrenomedullin (AM), a potent vasodilator peptide, improves elastase-induced emphysema (Murakami et al 2005). In this study, AM infusion significantly inhibited the increase in lung volume, static lung compliance, and mean linear intercept in mice given elastase. AM increased the numbers of mononuclear cells and sca-1-positive cells in circulating blood, and significantly increased the number of bone marrow-derived cells incorporated into the elastase-treated lung. *In vitro*, addition of AM attenuated elastase-induced cell death in alveolar epithelial cells and endothelial cells. These results suggest that AM improves emphysema at least in part through mobilization of bone marrow cells and direct protective effects on alveolar epithelial cells and endothelial cells. AM also ameliorated LPS-induced acute injury in rats (Itoh et al 2007), possibly through inhibition of inflammation, hyperpermeability, and alveolar wall cell apoptosis.

### Administration of exogenous stem/progenitor cells

After intravenous administration of lacZ-labeled bone marrow-derived cells into wild-type recipient mice with bleomycin-induced lung injury, cells were engrafted in recipient lung parenchyma with the phenotype of type I pneumocytes of the alveolar epithelium (Kotton et al 2001). On the other hand, male whole bone marrow cells or  $CD34^+lin^-$  bone marrow cells differentiated into bronchiolar epithelia and type II alveolar cells after transplantation into lethally irradiated female mice (Krause et al 2001; Theise et al 2002). Because differentiation into inflammatory cells was not observed, these findings suggest the potential

application of bone marrow-derived cells for therapy of lung diseases including COPD. However, several groups did not find evidence of pulmonary repopulation via bone marrow-derived cells (Davies et al 2002; Wagers et al 2002; Kotton et al 2005; Zander et al 2006), raising the possibility of a dominant role of resident lung stem cells in alveolar repair and regeneration.

Mesenchymal stem cells (MSC) reside in bone marrow (Friedenstein et al 1976), adipose tissue (Gimble and Guilak 2003), and many other tissues (Pittenger and Martin 2004). A recent study suggested that MSC reside in virtually all post-natal organs and tissues, and may be localized to vessel walls (da Silva Meirelles et al 2006). MSC can differentiate not only into osteoblasts, chondrocytes, and adipocytes, but also other types of cells such as vascular endothelial cells (Pittenger et al 1999). It has been demonstrated that transplanted MSC home to the lung in response to bleomycin-induced lung injury and adopt phenotypes of alveolar epithelial cells, endothelial cells, fibroblasts and bronchial epithelial cells, and protect lung tissue through suppression of proinflammatory cytokines such as TNF- $\alpha$  and IL-1, and through triggering production of reparative growth factors (Ortiz et al 2003; Rojas et al 2005; Ortiz et al 2007). Shigemura et al demonstrated that autologous transplantation of adipose tissue-derived MSC ameliorates pulmonary emphysema in rats (Shigemura et al 2006b), and accelerates alveolar and vascular regeneration after lung volume reduction surgery in rats with emphysema (Shigemura et al 2006a).

However, whether exogenous administration of those cells improves COPD in humans remains to be elucidated. In addition, recent studies demonstrated that cellular senescence is observed in epithelium and endothelium as well as in fibroblasts (Muller et al 2006; Tsuji et al 2006), raising the possibility that stem/progenitor cells are also associated with senescence (Sharpless and DePinho 2007). Accordingly, it is not clear which type of cells (including adult cells or embryonic cells) could be adopted for the treatment of COPD, and if it will be possible to repair emphysema or to prevent it.

### Importance of cigarette smoke cessation and exercise

Cigarette smoke causes apoptosis and an inflammatory response in the lower respiratory tract, impairs the repair functions of fibroblasts, epithelial cells and mesenchymal cells, and induces senescence of lung fibroblasts (Spurzem and Rennard 2005; Nyunoya et al 2006; Rennard et al 2006). Although a reduction in inflammation is observed

after smoking cessation in COPD patients, histopathological studies show persistent airway inflammation (Willemse et al 2004). Since cigarette smoke cessation improves respiratory symptoms and slows the rapid FEV<sub>1</sub> decline in COPD patients, it is apparent that cigarette smoke cessation is the primary therapeutic intervention for these patients, not only as therapeutic basis but also as ethical and economical viewpoints. However, the exact mechanism of the reduction in airway inflammation and the relationship with lung function and regeneration after cigarette smoke cessation remain to be established.

Exercise might be another approach, because mobilization of endothelial progenitor cells occurs after exercise (Rehman et al 2004). In addition, several studies have provided evidence that exercise improves several of the variables associated with poor outcomes such as exercise capacity and dyspnea as well as the multidimensional BODE index (Celli et al 2004; Cote and Celli 2005; Nici et al 2006). Therefore, it is interesting to speculate that the gain in exercise tolerance is achieved through mobilization of endothelial progenitor cells. Palange et al reported that circulating progenitor count was unchanged after endurance exercise in patients with COPD; however, this might have been due to insufficient intensity and/or duration of the test (Palange et al 2006).

## Conclusions

Growing evidence obtained from basic and translational research on regenerative medicine in COPD suggests that, in addition to cigarette smoking cessation and exercise, administration of humoral factors responsible for activation of endogenous stem/progenitor cells or administration of exogenous stem/progenitor cells may be a potential therapeutic tool in the treatment of COPD (Table 1). However, in addition to clarifying beneficial effects and their mechanism of

tissue repair and regeneration by administration of humoral factors or exogenous stem/progenitor cells, harmful aspects including tumor formation should be carefully assessed. Therefore, we are at a very initial stage, and tissue regeneration for COPD patients, although very attractive, is still a far away option.

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## Disclosures

Neither author has any conflicts of interest to disclose.

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**Table 1** Potential strategies for tissue regeneration in COPD

1. Administration of growth/differentiation factors
  - ATRA
  - FGF-2
2. Activation of endogenous stem/progenitor cells
  - HGF
  - AM
  - G-CSF
3. Administration of exogenous stem/progenitor cells
  - MSC (bone marrow, fat tissue)
  - Bone marrow-derived cells (?)
  - EPC (?)

**Abbreviations:** G-CSF, granulocyte-colony stimulating factor; HGF, hepatocyte growth factor; AM, adrenomedullin; MSC, mesenchymal stem cells; EPC, endothelial progenitor cells; FGF-2, fibroblast growth factor; ATRA, all-trans retinoic acid.

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