Therapeutic Advances in Respiratory Disease *Review*

Stem cell therapy: the great promise in lung disease

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***Abstract*:** Lung injuries are leading causes of morbidity and mortality worldwide. Pulmonary diseases such as asthma or chronic obstructive pulmonary disease characterized by loss of lung elasticity, small airway tethers, and luminal obstruction with inflammatory mucoid secretions, or idiopathic pulmonary fibrosis characterized by excessive matrix deposition and destruction of the normal lung architecture, have essentially symptomatic treatments and their management is costly to the health care system.
Regeneration of tissue by stem cells from endogenous, exogenous, and even genetically modified cells is a promising novel therapy. The use of adult stem cells to help with lung regeneration and repair could be a newer technology in clinical and regenerative medicine. In fact, different studies have shown that bone marrow progenitor cells contribute to repair and remodeling of lung in animal models of progressive pulmonary hypertension.
Therefore, lung stem cell biology may provide novel approaches to therapy and could represent a great promise for the future of molecular medicine. In fact, several diseases can be slowed or even blocked by stem cell transplantation.

***Keywords*:** Stem cells, cell-based therapy, lung diseases, human

Introduction

Chronic pulmonary diseases, such as chronic obstructive pulmonary disease and asthma, or interstitial lung diseases, such as idiopathic pulmonary fibrosis (IPF) and lung cancer, are leading causes of morbidity and mortality worldwide (MacCallum, 2005). It has been estimated that in the US alone, more than 35 million Americans have chronic lung diseases (National Center for Health Statistics), and every year over 349,000 Americans die from lung disease (US Centers for Disease Control and Prevention, 2002). In Europe, the European Lung Foundation and the European Respiratory Society predict an increase in the number of deaths from lung diseases between now and 2020, in particular from chronic obstructive pulmonary disease (COPD), lung cancer and tuberculosis (TB). Based on their prediction, in 2020, 11.9 million out of 68 million deaths worldwide, will be caused by lung diseases (4.7 by COPD, 2.5 by pneumonia, 2.4 by TB and 2.3 million by lung cancer). Respiratory diseases rank second (after cardiovascular diseases) in terms of mortality, incidence, prevalence, and costs. In the UK, they are already the leading killer (European Lung Foundation).

The annual economic burden of respiratory diseases in Europe is estimated to be approximately €102 billion or €118 per capita. The factors costing the most are lost workdays (a total of ~66,155 work days per 100,000 population are lost annually), accounting for €48.3 billion or 47.4%, and inpatient care €17.8 billion or 17.5%. Outpatient care contributes a further €9.1 billion (8.9%) and prescription drugs add €6.7 billion (6.6%) including VAT.

Premature mortality and rehabilitation are estimated to contribute another €20.0 billion (19.6%) (European Lung Foundation). Asthma and COPD are inflammatory lung diseases characterized, respectively, by reversible and irreversible airflow obstruction and airway hyperresponsiveness/hyperreactivity and chronic inflammation characterized by an influx and activation of inflammatory cells, generation of inflammatory mediators, epithelial cell shedding and remodeling of lung parenchyma

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(Kirkham *et al.* 2006). The human and societal toll of COPD is considerable, and there is a clear need for better prevention and early detection/intervention, including more specific and effective therapies for all stages of the disease.

The key pathologic changes underlying the physiological hallmarks of COPD include the loss of lung elasticity and small airway tethers (emphysema), thickening of the small airway wall to reduce caliber and luminal obstruction with inflammatory mucoid secretions (Hogg, 2004). Airway epithelial cells respond dynamically to the inciting stimuli and are the focus of viral and bacterial infections that exacerbate COPD and accelerate deterioration of lung function. Epithelial hyperplasia, mucous secretory cell hyperplasia, squamous metaplasia, and mucus accumulation must result from disruptions in normal cell and tissue dynamics caused by both the initial stimuli and the spiral of infectious complications (Randell, 2006). It has been hypothesized that endothelial dysfunction might be an initiating event that promotes vessel remodeling in COPD. VEGF-mediated apoptosis of endothelial, causing loss of capillaries, may well be a central mechanism in patients with emphysema and muscle wasting (Siafakas *et al.* 2007).

IPF is one of the group of interstitial lung diseases that are characterized by excessive matrix deposition and destruction of the normal lung architecture. Although, the precise etiology is unknown, a number of risk factors may contribute to disease development, including smoking, drug exposure, infectious agents, and genetic predisposition.

The primary effector cells in fibrosis are the myofibroblasts that produce collagen, have a contractile phenotype, and are characterized by the presence of alpha-smooth muscle actin stress fibers. They may be derived by activation/proliferation of resident lung fibroblasts, epithelial-mesenchymal differentiation, or recruitment of circulating fibroblastic stem cells (fibrocytes)(Scotton *et al.* 2007). Histologically, IPF lungs have alternating regions of normal lung parenchyma, interstitial inflammation, fibrosis, and 'honeycombing.' These features are a result of failed alveolar reepithelialization, fibroblast persistence, and excessive deposition of collagen and other extracellular matrix (ECM) components, leading to irreversible loss of lung function.

From a therapeutic viewpoint, interfering with the pathways that lead to myofibroblast expansion should be of considerable benefit in the treatment of IPF.

Lung cancer is the leading cause of death due to cancer all over the world and the five-year survival rate remains relatively poor despite aggressive medical therapy (Yanagi *et al.* 2007). As with most of the cancers, lung cancer appears to arise by a transformation of organ-specific stem cells or progenitor cells that results in the selective expression of genes enhancing self-renewal potential (Giangreco *et al.* 2007; Reya *et al.* 2001).

Usually, most lung diseases involve a combination of these categories, such as emphysema, which involves both airflow obstruction and oxygenation problems.

The pulmonary system contains a variety of epithelial cell populations. The alveolar epithelium is composed of alveolar type II (AT2) cells, the cuboidal epithelial cells that produce surfactants and the resulting surface tension required for gas exchange, as well as the alveolar type I (AT1) cells, the flat epithelial cells that deliver oxygen to the blood. Numerous stromal cells are present, and the lung has been described as containing at least 40 different cell types, likely to be an underestimation given the promise of future studies to identify distinct stem, progenitor, and differentiated cells (Carla, 2007). Considering that chronic pulmonary diseases have essentially symptomatic treatments is often associated with failure, aside from lung transplant, and that the management of lung diseases is costly to the health care system (US National Heart, Lung and Blood Institute, 2004), lung stem cell biology may provide novel approaches to therapy.

Stem cells

Nowadays, stem cell therapy represents the great promise for the future of molecular medicine. Several diseases can be slowed or even blocked by stem cell transplantation (SCT).

Because lung diseases are associated with tissue disruption (Shimabukuro *et al.* 2003), the capacity of stem cells to repair the damaged tissue open a huge way to their use as optimal tool to treatment. Among the stem cell population, mesenchymal stem cells (MSCs) probably have the best results in medical research. These cells

are nonhematopoietic stem cells having a multilineage potential, as they have the capacity of differentiating into both mesenchymal and nonmesenchymal lineages. MSCs are a population of progenitor cells of mesodermal origin found principally in the bone marrow of adults, giving rise to skeletal muscle cells, blood, fat, vascular, and urogenital systems, and to connective tissues throughout the body (Beyer Nardi and da Silva Meirelles, 2006; Sethe, 2006). MSCs can be isolated from different tissues other than bone marrow: adipose tissue, liver, tendons, synovial membrane, amniotic fluid, placenta, umbilical cord, and teeth (Phinney and Isakova, 2005). MSCs show a high-expansion potential, genetic and phenotypic stability, can be easily collected and shipped from the laboratory to the bedside, and are compatible with different delivery methods and formulations (Giordano *et al.* 2007). In addition, MSCs have two other extraordinary characteristics: they are able to migrate to sites of tissue injury and have strong immunosuppressive properties that can be exploited for successful autologous as well as heterologous transplantations (Le Blanc and Pittenger, 2005). Besides, MSCs are easily isolated from a small aspirate of bone marrow and expanded with high efficiency. Adult bone marrow-derived stem cells have great plasticity and are able to differentiate into bronchial and alveolar epithelium, vascular endothelium, and interstitial cell types, making them prime candidates for lung-tissue repair (Loebinger and Janes, 2007; Yen *et al.* 2006). Regeneration of tissue by stem cells, from endogenous, exogenous and even genetically modified cells is a promising novel therapy (Hedrick and Deniels, 2003). The use of adult stem cells could be a newer technology in clinical and regenerative medicine, and so MSCs could be the novel 'cell-based drug' for the lung disease therapeutic management.

Stem cells in lung diseases: state of the art

Injury models have suggested that functionally distinct epithelial stem cell populations exist in precise anatomical locations in the lung (Kim, 2005). Each of the tracheobronchial and alveolar airway regions consists of distinct epithelial cell types with unique cellular physiologies and stem cell compartments (Liu *et al.* 2006). In fact, it has been reported and frequently cited that the lung contains 40 different cell types but current analyses, however, suggest that this number may be a gross underestimate, since new endogenous lung cell populations and circulating transient cells found in the lung have been identified (Kim, 2007).

A variety of recent studies in mice have suggested that marrow stem cells can serve as progenitors of differentiated cells of solid organs; these findings have challenged long-held views regarding the fixed nature of adult stem cell potential and suggest the possibility of circulating tissue stem cells (Kotton *et al.* 2004).

Although, it is known that MSCs differentiate into osteoblasts, chondroblasts, adipocytes, and hematopoietic supporting stroma, recent reports suggest that they can also differentiate into nonstromal tissues, including lung epithelial cells. Indeed, it has been shown that stem cells have the ability to differentiate and function as both airway and lung parenchyma epithelial cells in both *in vitro* and *in vivo* experiments (Loebinger *et al.* 2008). The potential for deriving respiratory cell types from stem cells for treatment of respiratory diseases strongly suggests that stem cell derivatives may be used for lung replacement/regeneration therapeutics (Olsson *et al.* 2007).

These data provide a strong rationale to explore the potential use of MSCs for the treatment of lung diseases (Conese and Rejman, 2006; Wang *et al.* 2005). For example, in cystic fibrosis (CF) caused by mutations of CF transmembrane conductance regulator (CFTR), MSCs could be used to restore the abnormal CFTR function.

Different studies have shown that both human and mouse embryonic stem (ES) cells and MSCs derived from either adult mouse or human bone marrow or from human umbilical cord blood, can be induced to express markers of airway or alveolar epithelial phenotype *in vitro* (Eastham *et al.* 2007). In some of these studies, it has been recently demonstrated that bone marrow progenitor cells contribute to repair and remodeling of the lung in a rat model of progressive pulmonary hypertension (Spees *et al.* 2008).

MSCs could take a more relevant role in lung modulating of local inflammatory and immune responses (Weiss, 2007).

Although, there are some studies concerning the safety and effectiveness of using the

endothelial progenitor cells (EPCs) in patients with idiopathic pulmonary arterial hypertension (University of Michigan Cancer Center, Northern Therapeutics and Zhejiang University), there have not yet been clinical trials on the use of MSCs in lung disease.

Recently, Gazdhar *et al.* have presented at the European Respiratory Society Congress, held in Stockholm in September 2007, an interesting study on the bone marrow derived MSCs accelerating alveolar epithelial repair *in vitro* (Gazdhar *et al.* 2007).

Moreover, Lane *et al.* support a potential role in cell therapy for lung diseases for differentiated embryonic stem cells (ESCs), enriched for a specific phenotype (Lane, 2007).

Overall, stem cell therapy could show some problems: side effects, bacterial, and viral infections carried by the donor cells, allergic reactions. For example, Streptococcus pneumoniae (*S. pneumoniae*) may cause severe and lethal infections months and years following SCT, especially in allogeneic patients, and particularly those with GVHD (Benjamin *et al.* 2002; Engelhard *et al.* 2002; Runde *et al.* 2001).

Moreover, Bronchiolitis obliterans organizing pneumonia (BOOP) has been reported following hematopoietic stem cell (HSC) transplantation (Hildebrandt *et al.* 2008). Histologic BOOP may be idiopathic or it may be associated with bacterial and viral infections, drugs, collagen vascular diseases, aspiration, irradiation, inflammatory bowel disease, myelodysplastic syndrome, common variable immunodeficiency syndrome, and lung transplantation (Freudenberger *et al.* 2003). However, there remains little information about the clinical presentation of BOOP in this population, and the risk factors for the development of this condition have not been defined and quantified in an analytic study. Therefore, deep and exhaustive studies to find out the exact biology of stem cells are absolutely needed in the near future for a better use of these stem cells in regenerative medicine, as well as in lung disease treatment.

The website www.Clinical.Trials.gov of the United States National Institute of Health provides information on the current clinical trials based on the use of MSCs for lung diseases.

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Conflict of interest

None declared.

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