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MINIREVIEWS

New therapies for chronic obstructive pulmonary disease, lung regeneration

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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by the presence of airflow limitations that are not fully reversible and is a major cause of chronic morbidity and mortality worldwide. Although there has been extensive research examining the molecular mechanisms underlying the development of COPD, there is no proven clinically effective treatment for promoting recovery from established COPD. At present, regeneration is the only hope for a cure in patients with COPD. In this article, we review current treatments for COPD, focusing particularly on recent advances in lung regeneration based on two major approaches: regeneration-promoting agents and cell therapy. Retinoic acids are the major focus among regeneration-promoting agents, while mesenchymal stem cells are the main topic in the field of cell-based therapy. This article aims to provide valuable information for developing new therapies for COPD.

Key words: Emphysema; Chronic inflammation; Stem cell; Retinoic acid; Type Ⅱ cells

Core tip: There is currently no proven clinically effective treatment for achieving recovery from established emphysema. At present, regeneration is the only hope for a cure in patients with chronic obstructive pulmonary disease (COPD). In this article, we review current treatments for COPD, focusing particularly on recent advances in lung regeneration. This article aims to provide valuable information for developing new therapies for COPD.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a slowly progressive respiratory disease characterized by irreversible airflow limitations[1-3]. COPD is a major cause of morbidity and mortality worldwide and is COPD primarily characterized by two distinctive criteria: chronic bronchitis and pulmonary emphysema. Chronic bronchitis results from the inhalation of toxic particles, gases and/or cigarette smoke, which subsequently produces a cough and sputum. Pulmonary emphysema is defined as enlargement of the distal airspace due to

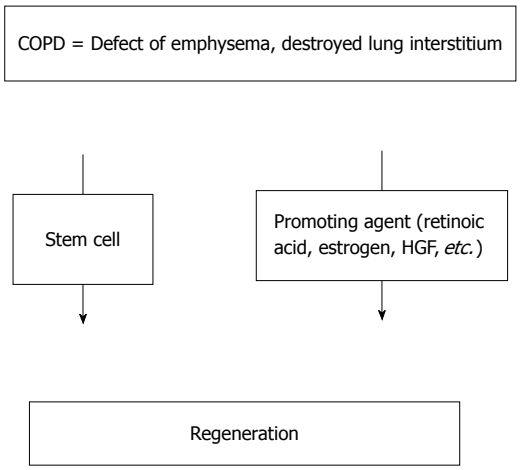

Figure 1 Schematic representation of the use of regeneration strategies to treat chronic obstructive pulmonary disease. COPD: Chronic obstructive pulmonary disease; HGF: Hepatocyte growth factor.

destruction of the airway wall[4]. Cigarette smoking is the main etiological factor in this condition, although only 10% to 20% of smokers develop clinically significant COPD. Factors associated with the degree of susceptibility to COPD are considered to be responsible for this variation[5]. Although there has been extensive research examining the molecular mechanisms underlying the development of emphysema, the clinical management of patients with pulmonary emphysema remains mostly supportive. In addition, there is currently no proven clinically effective treatment for achieving a recovery from established emphysema[6,7].

At present, regeneration of the lungs provides the only hope for a cure for COPD. Methods to promote lung regeneration have the potential to alter the natural history of COPD. Such methods include the use of retinoids and mesenchymal stem cell therapy (Figure 1). All-trans-retinoic acid (ATRA) has been reported to rescue the lungs in rats with elastase-induced emphysema and was the first agent reported to promote lung regeneration in a model of emphysema[8]. Recently, stem cell therapy was shown to promote lung regeneration. In this article, we review current treatments for COPD, focusing particularly on recent advances associated with lung regeneration.

CURRENT THERAPIES FOR COPD

Some treatments can be used to control the symptoms and/or sometimes slow the progression of COPD. However, unfortunately, the symptoms of COPD cannot be completely relieved with currently available treatments and typically progresses gradually. One of the most important treatments for COPD is for current smokers to stop smoking.

Bronchodilators are the mainstay of treatment for COPD. These drugs open the airways and decrease sputum production; inhaled bronchodilators are usually administered. There are several types of bronchodilators: short-acting beta agonists and anticholinergics are used to treat mild COPD, while long-acting treatments, such as long-acting beta agonists, anticholinergics or a combination of these agents, are often recommended in cases of moderate COPD. Theophylline can be given orally, and inhaled glucocorticoids may be used for frequent COPD exacerbation and/or in patients with bronchial asthma. In cases of advanced COPD, patients exhibiting hypoxemia are often supplied oxygen therapy, which may improve their survival and quality of life. Pulmonary rehabilitation programs are also important and can be effective in relieving shortness of breath. Lung volume reduction surgery and/or lung transplantation are performed in selected patients with COPD, and vaccination against the flu and pneumococci is also recommended[7].

Novel therapies are currently being developed for COPD. Smoking cessation is fundamental, and new treatments in this field include antinicotine vaccines, cannabinoid receptor antagonists and dopamine D3 receptor antagonists. Anti-inflammatory drugs are also in development to reduce airway inflammation, including kinase inhibitors, chemokine receptor antagonists, innate immune mechanism inhibitors and statins. Antioxidants, mucolytics, antiproteases and antifibrotics are all under active development as well[9]. However, these new treatments are still considered to be insufficient to completely cure COPD, since they are merely modifications of previously established therapies. Nevertheless, lung regeneration may make it possible for damaged lung tissue to recover, eventually becoming healthy.

OVERVIEW OF LUNG REGENERATION

Regeneration is the process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish a normal function. Approaches to aid in lung regeneration in patients with COPD aim to correct the defects associated with emphysema and replace the destroyed lung interstitium. However, inducing regeneration in the lungs has proven to be difficult, as these organs display a complex three-dimensional system. Moreover, the lungs consist of more than 40 different cell types.

In experimental animal models, the degree of lung recovery depends on species and age. Generally speaking, small animals show more capacity for healing than large animals[10]. For example, the weight of the remaining lung doubles within 14 d after pneumonectomy in rats[11], whereas a period of 28 d 5 mo period is needed in dogs[13]. Age is another important factor affecting the capacity for lung recovery. Kenzaki *et al*[14] implanted fetal lung tissue fragments into adult rat lungs and found regeneration by the fetal lung tissue, but not the adult lung tissues.

Human lungs have a regenerative capacity, as demonstrated in Nepalese children given maternal vitamin A supplements[15]. In addition, lung regeneration

was observed in an adult patient treated with pneumonectomy[16]. The possibility of lung regeneration in cases of COPD has been sought in several settings[17,18]. For example, Butler demonstrated a case in which the patient showed an increase in vital capacity after undergoing resection of lung cancer. The authors hypothesized that, reminiscent of the role of stretching in lung development[16,19], cyclic stretching may be an important trigger for new lung growth. These findings suggest that new lung growth may occur in adult humans.

At present, regeneration is possible. In fact, there are two treatments for inducing regeneration in the lungs: regeneration-promoting agents, such as retinoic acid, and cell therapy, such as that using stem cells.

REGENERATION-PROMOTING AGENTS

Several lines of evidence support the concept that alveolar repair, including the formation of a new alveolar wall, is possible in adult mammals. ATRA has been reported to recover elastase-induced emphysema[8] based on results showing the attenuation of alveolar destruction and increases in the number of alveoli. RA is known to play a variety of roles in embryonic branching morphogenesis[20] and is required for the formation of normal alveoli and alveolar elastic fibers in mice[21] as well as elastin synthesis[22]. However, the degree of RA-induced lung regeneration is dependent on age. We previously reported that RA does not produce alveologenesis in adult mice[23,24]. Aging is one cause of the discrepancies observed among different studies employing RA administration.

In addition, the results of a clinical trial of the efficacy of ATRA in the treatment of COPD were recently reported in which a double-blind placebo-controlled clinical trial of ATRA was performed in patients with moderate to severe COPD[25,26]. Notably, ATRA reduced the MMP-9 level and increased the TIMP-1 level, resulting in modulation of the protease/antiprotease balance in COPD patients[27]. However, neither physiologic nor CT measurements changed appreciably in response to the therapy. The REPAIR (Retinoid treatment of Emphysema in Patients on the Alpha-1 antitrypsin International Registry) trial was an investigator-initiated, double-blind, placebo-controlled randomized study performed to assess the safety and efficacy of a selective agonist of the gamma-type retinoic acid receptor in emphysema patients with alpha-1 antitrypsin deficiency. However, no significant treatment differences were found in most of the functional parameters[28]. The TESRA (Treatment of Emphysema with a Selective Retinoid Agonist) study, another trial using a retinoid agonist in COPD patients, was recently conducted and found that the administration of palovarotene, a retinoic agonist, significantly reduced the decline in DLco and FEV1 in patients with lower lobe emphysema[29]. The results of these clinical studies indicate that retinoic acid treatment does not result in any improvements in human COPD patients.

Although estrogens are considered to be responsible for sexual development, their effects beyond the reproductive system are becoming increasingly recognized. A recent study demonstrated that estrogen has a regulatory role in alveolar formation in which estrogen receptor-alpha and estrogen receptor-beta are required for the formation of a full complement of alveoli in female mice. This loss of alveoli may be reversed by estrogen replacement[30], and estradiol replacement slows the rate of decline in the lung function in females with COPD[31].

Adrenomedullin (AM) was initially identified to be a vasodilator. It is found in many tissues, including airway basal cells and type Ⅱ cells of the lungs[32] and promotes angiogenesis in addition to having protective effects on the cardiovascular and respiratory systems[33]. AM antagonists decrease the lung capillary density and impair alveolar development, whereas AM attenuates arrested lung angiogenesis[34]. Furthermore, treatment with AM improves elastase-induced emphysema in mice[35] and AM has recently been shown to be effective for treating pulmonary hypertension in humans[36,37].

Although hepatocyte growth factor (HGF) is a growth factor for hepatocytes *in vitro*[38], it also stimulates type II cells and endothelial cells both *in vitro* and *in vivo* in the lungs[39,40]. Intranasal treatment with HGF reverses the physiological and morphometric changes associated with lung emphysema in mice[41].

Granulocyte colony-stimulating factor (G-CSF) stimulates the bone marrow to produce granulocytes and stem cells. Treatment with G-CSF promotes recovery of the exercise capacity and regeneration of alveolar structural alterations in emphysematous mice[42]. However, G-CSF has no effect in a dexamethasone model of alveolar insufficiency[43].

Keratinocyte growth factor (KGF), also known as fibroblast growth factor-7, favorably influences alveolar maintenance and repair and possesses anti-inflammatory properties. The administration of KGF before, but not after, treatment protects against elastase-induced pulmonary inflammation, MMP activation, alveolar cell DNA damage and subsequent emphysema in mice[44].

The 3-hydroxy-3 methyl glutaryl coenzyme A reductase inhibitor, simvastatin has been shown to reverse emphysema in adult mice with elastase-induced emphysema, with a reduction in the mean linear intercept[45]. However, a human clinical study did not demonstrate any beneficial effects on the acute exacerbation of COPD[46].

CELL THERAPY

Stem cells (SC), including mesenchymal stem cells (MSCs), and embryonic stem (ES) cells, are mainly used for regeneration as cell therapy. Mouse embryonic stem cells differentiate into alveolar type Ⅱ cells following endotracheal injection[47]. Alveolar type Ⅱ cells are important because they differentiate into

alveolar epithelial type Ⅰ cells in damaged lungs and are successfully derived from human ES cells[48]. The use of induced pluripotent stem (iPS) cells is also hopeful in areas of regeneration, similar to human ES cells.

MSCs are stromal cells that can be readily attained from adult bone marrow and adipose tissue in addition to umbilical cords. MSCs have been shown to be capable of differentiating into a variety of cell types, including endothelial, epithelial and neuronal cells as well as adipocytes, depending on the culture conditions[18,49]. MSCs are able to proliferate and migrate to sites of injury and can differentiate into a variety of cell types in the lungs, including type Ⅰ and type Ⅱ pneumocytes and myofibroblasts[50-52]. Human amniotic fluid stem cells are produced in response to lung damage in order to express specific alveolar versus bronchiolar epithelial cell lineage markers, such as thyroid transcription factor 1, surfactant protein C and Clara cell 10-kDa proteins[53]. Since the rates of engraftment obtained using exogenous MSCs are too low to achieve cellular replacement of damaged tissue[54,55], the paracrine effect of MSCs is now suggested to be the major mechanism of action. The administration of MSCs results in anti-inflammatory and immunomodulatory activities both *in vitro* and *in vivo*. These anti-inflammatory effects are mediated by transforming growth factor beta, prostaglandin E2, interleukin 10 and indoleamine 2; 3-dioxygenase[49,56]. MSCs also have immunomodulatory effects *via* the inhibition of T-cell and B-cell proliferation, natural killer cell and cytotoxic T lymphocyte activation and antigen-presenting functions[49,56].

A clinical trial to assess COPD regeneration using MSCs was recently conducted in which the safety and efficacy of an Ⅳ preparation of allogeneic MSCs (Prochymal) was evaluated[57]. Although there were no significant differences in lung function parameters, the levels of C-reactive protein, an indicator of systemic inflammatory responses, were decreased in some subjects. Another approach applying MSCs is to populate a biological connective tissue scaffold, which can then be used to grow autologous tissue prior to surgical implantation[58].

Research on lung-specific stem cells is also ongoing. Alveoli consist of many type Ⅰ epithelium cells and a small amount of type Ⅱ epithelium cells; type Ⅱ epithelium cells differentiate into type Ⅰ epithelium cells. Damage to type Ⅱ epithelium cells has been reported in lungs exhibiting COPD[59,60], and the intratracheal instillation of type Ⅱ cells attenuates bleomycin-induced fibrosis in rats[61]. In a previous study, progenitor cells were isolated from adult human lungs with the ability to differentiate into alveolar type Ⅱ cells[62]. In addition, the role of endothelial progenitor cells (EPCs) in the pathogenesis of pulmonary hypertension has been investigated[63]. The use of these lung-specific cell approaches is hopeful, as endothelial dysfunction and reduced levels of circulating EPCs are observed in COPD patients[64,65].

All tissues and organs are made up of cells and the associated extracellular matrix- a secreted product of the resident cells consisting of a unique tissue-specific three-dimensional environment containing structural and functional molecules. Due to the complex three-dimensional architecture and structure-function relationships observed in the lungs, as well as the large number of differentiated cell types present in lung tissues, *ex-vivo* lung bioengineering is expected to be a difficult task compared with bioengineering of the trachea or larynx.

Hence, a number of trials involving decellularization, recellularization, biomechanical stabilization and implantation approaches for application in the lungs are under investigation[66,67].

FUTURE DIRECTIONS

At present, the investigation of many regenerative approaches is underway, although none of these therapies are able to recover functional impairments in COPD patients. Several breakthroughs are clearly needed, especially with respect to rebuilding the three-dimensional organ architecture and identifying lung stem cell populations. It is necessary to clarify the inflammatory processes underlying the modulation of inflammation and promotion of tissue repair, and care should be taken to address issues regarding the optimal source, methodology, route and timing of administration as well as costs[10,49]. We are hopeful that these problems will be overcome in the future and that therapies promoting lung regeneration will make it possible for patients to recover from COPD.

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