**Name of journal: *World Journal of Respirology***

**ESPS Manuscript NO: 14115**

**Columns: MINIREVIEWS**

**New therapies for COPD, lung regeneration**

Fujita M. Regeneration for COPD

Masaki Fujita

**Masaki Fujita,** Department of Respiratory Medicine, Faculty of Medicine, Fukuoka University, Fukuoka 814-0180, Japan

**Author contributions:** Fujita M solely contributed to this paper.

**Conflict-of-interest:** The authors declare that they have no competing interests.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** **Masaki Fujita, MD, PhD,** Department of Respiratory Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonanku, Fukuoka 814-0180, Japan. mfujita@fukuoka-u.ac.jp

**Telephone:** +81-92-8011011

**Fax:** +81-92-8656220

**Received:** September 20, 2014

**Peer-review started:** September 20, 2014

**First decision:** November 27, 2014

**Revised:** November 15, 2014

**Accepted:** Janurary 15, 2015

**Article in press:**

**Published online:**

**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

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tips:** 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.

Fujita M. New therapies for COPD, lung regeneration. *World J Respirol* 2015; In press

**INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is a slowly progressiverespiratory disease characterized by irreversible airflow limitations[[1](http://pats.atsjournals.org/cgi/content/full/2/4/258%22%20%5Cl%20%22BIB1#BIB1)-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 bronchitisresults 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 destruction of theairway wall[4]. Cigarette smoking is the main etiological factorin this condition, althoughonly 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 days after pneumonectomy in rats[11], whereas a period of 28 days is required for the same effect in rabbits[12] and a five-month 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 hypertensionhas 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.

**ACKNOWLEDGEMENTS**

We appreciate the assistance of Dr. Brian Quinn in editing the use of the English language.

**REFERENCES**

1 **Celli BR**, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; **23**: 932-946 [PMID: 15219010 DOI: 10.1183/09031936.04.00014304]

2 Global strategy for diagnosis, management, and prevention of COPD. Cited 2014-01. Available from: URL: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html

3 **Hogg JC**. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004; **364**: 709-721 [PMID: 15325838 DOI: 10.1016/S0140-6736(04)16900-6]

4 **Snider GL,** Kleinerman LJ, Thurlbeck WM, Bengali ZH. The definition of emphysema. Report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases workshop. *Am Rev Respir Dis* 1985; **132**: 182-185 [PMID: 4014865]

5 **Hogg JC**, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968; **278**: 1355-1360 [PMID: 5650164 DOI: 10.1056/NEJM196806202782501]

6 **Hogg JC**. A stimulating treatment for emphysema. *Nat Med* 1997; **3**: 603-604 [PMID: 9176480 DOI: 10.1038/nm0697-603]

7 **Ferguson GT,** Make B. Management of stable chronic obstructive pulmonary disease. Stoller JK, editor. Waltham, MA: UpTo Date, 2014

8 **Massaro GD**, Massaro D. Retinoic acid treatment abrogates elastase-induced pulmonary emphysema in rats. *Nat Med* 1997; **3**: 675-677 [PMID: 9176496 DOI: 10.1038/nm0697-675]

9 **Ross CL**, Hansel TT. New drug therapies for COPD. *Clin Chest Med* 2014; **35**: 219-239 [PMID: 24507848 DOI: 10.1016/j.ccm.2013.10.003]

10 **Kubo H**. Concise review: clinical prospects for treating chronic obstructive pulmonary disease with regenerative approaches. *Stem Cells Transl Med* 2012; **1**: 627-631 [PMID: 23197868 DOI: 10.5966/sctm.2012-0065]

11 **Nijjar MS**, Thurlbeck WM. Alterations in enzymes related to adenosine 3',5'-monophosphate during compensatory growth of rat lung. *Eur J Biochem* 1980; **105**: 403-407 [PMID: 6247152 DOI: 10.1111/j.1432-1033.1980.tb04514.x]

12 **Cowan MJ**, Crystal RG. Lung growth after unilateral pneumonectomy: quantitation of collagen synthesis and content. *Am Rev Respir Dis* 1975; **111**: 267-277 [PMID: 1119740]

13 **Hsia CC**, Herazo LF, Fryder-Doffey F, Weibel ER. Compensatory lung growth occurs in adult dogs after right pneumonectomy. *J Clin Invest* 1994; **94**: 405-412 [PMID: 8040282 DOI: 10.1172/JCI117337]

14 **Kenzaki K**, Sakiyama S, Kondo K, Yoshida M, Kawakami Y, Takehisa M, Takizawa H, Miyoshi T, Bando Y, Tangoku A, Liu M. Lung regeneration: implantation of fetal rat lung fragments into adult rat lung parenchyma. *J Thorac Cardiovasc Surg* 2006; **131**: 1148-1153 [PMID: 16678603 DOI: 10.1056/NEJMoa0907441]

15 **Checkley W**, West KP, Wise RA, Baldwin MR, Wu L, LeClerq SC, Christian P, Katz J, Tielsch JM, Khatry S, Sommer A. Maternal vitamin A supplementation and lung function in offspring. *N Engl J Med* 2010; **362**: 1784-1794 [PMID: 20463338 DOI: 10.1056/NEJMoa0907441]

16 **Butler JP**, Loring SH, Patz S, Tsuda A, Yablonskiy DA, Mentzer SJ. Evidence for adult lung growth in humans. *N Engl J Med* 2012; **367**: 244-247 [PMID: 22808959 DOI: 10.1056/NEJMoa1203983]

17 **Rennard SI**, Wachenfeldt Kv. Rationale and emerging approaches for targeting lung repair and regeneration in the treatment of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2011; **8**: 368-375 [PMID: 21816994 DOI: 10.1513/pats.201102-019RM]

18 **Hind M**, Maden M. Is a regenerative approach viable for the treatment of COPD? *Br J Pharmacol* 2011; **163**: 106-115 [PMID: 21265829 DOI: 10.1111/j.1476-5381.2011.01246.x]

19 **Brody JS,** Thurlbeck WM. Development, growth, and aging of the lung. In: Macklem PT, Mead J, eds. Handbook of　physiology - the respiratory system: mechanics of breathing. Bethesda, MD: American Physiological Society, 1986: 355-386

20 **Malpel S**, Mendelsohn C, Cardoso WV. Regulation of retinoic acid signaling during lung morphogenesis. *Development* 2000; **127**: 3057-3067 [PMID: 10862743]

21 **McGowan S**, Jackson SK, Jenkins-Moore M, Dai HH, Chambon P, Snyder JM. Mice bearing deletions of retinoic acid receptors demonstrate reduced lung elastin and alveolar numbers. *Am J Respir Cell Mol Biol* 2000; **23**: 162-167 [PMID: 10919981 DOI: 10.1165/ajrcmb.23.2.3904]

22 **Liu B**, Harvey CS, McGowan SE. Retinoic acid increases elastin in neonatal rat lung fibroblast cultures. *Am J Physiol* 1993; **265**: L430-L437 [PMID: 8238530]

23 **Fujita M**, Ye Q, Ouchi H, Nakashima N, Hamada N, Hagimoto N, Kuwano K, Mason RJ, Nakanishi Y. Retinoic acid fails to reverse emphysema in adult mouse models. *Thorax* 2004; **59**: 224-230 [PMID: 14985558 DOI: 10.1136/thx.2003.010785]

24 **Fujita M**, Nakanishi Y. The pathogenesis of COPD: lessons learned from in vivo animal models. *Med Sci Monit* 2007; **13**: RA19-RA24 [PMID: 17261992]

25 **Mao JT**, Goldin JG, Dermand J, Ibrahim G, Brown MS, Emerick A, McNitt-Gray MF, Gjertson DW, Estrada F, Tashkin DP, Roth MD. A pilot study of all-trans-retinoic acid for the treatment of human emphysema. *Am J Respir Crit Care Med* 2002; **165**: 718-723 [PMID: 11874821 DOI: 10.1164/ajrccm.165.5.2106123]

26 **Roth MD**, Connett JE, D'Armiento JM, Foronjy RF, Friedman PJ, Goldin JG, Louis TA, Mao JT, Muindi JR, O'Connor GT, Ramsdell JW, Ries AL, Scharf SM, Schluger NW, Sciurba FC, Skeans MA, Walter RE, Wendt CH, Wise RA. Feasibility of retinoids for the treatment of emphysema study. *Chest* 2006; **130**: 1334-1345 [PMID: 17099008 DOI: 10.1378/chest.130.5.1334]

27 **Mao JT**, Tashkin DP, Belloni PN, Baileyhealy I, Baratelli F, Roth MD. All-trans retinoic acid modulates the balance of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in patients with emphysema. *Chest* 2003; **124**: 1724-1732 [PMID: 14605041 DOI: 10.1378/chest.124.5.1724]

28 **Stolk J**, Stockley RA, Stoel BC, Cooper BG, Piitulainen E, Seersholm N, Chapman KR, Burdon JG, Decramer M, Abboud RT, Mannes GP, Wouters EF, Garrett JE, Barros-Tizon JC, Russi EW, Lomas DA, MacNee WA, Rames A. Randomised controlled trial for emphysema with a selective agonist of the γ-type retinoic acid receptor. *Eur Respir J* 2012; **40**: 306-312 [PMID: 22282548 DOI: 10.1183/09031936.00161911]

29 **Jones PW,** Rames D. TESRA (Treatment of Emphysema with a Selective Retinoid Agonist) study results. *Am J Respir Crit Care Med* 2011; **183**: A6418

30 **Massaro D**, Massaro GD. Estrogen regulates pulmonary alveolar formation, loss, and regeneration in mice. *Am J Physiol Lung Cell Mol Physiol* 2004; **287**: L1154-L1159 [PMID: 15298854 DOI: 10.1152/ajplung.00228.2004]

31 **Carlson CL**, Cushman M, Enright PL, Cauley JA, Newman AB. Hormone replacement therapy is associated with higher FEV1 in elderly women. *Am J Respir Crit Care Med* 2001; **163**: 423-428 [PMID: 11179117 DOI: 10.1164/ajrccm.163.2.2003040]

32 **Martínez A**, Miller MJ, Catt KJ, Cuttitta F. Adrenomedullin receptor expression in human lung and in pulmonary tumors. *J Histochem Cytochem* 1997; **45**: 159-164 [PMID: 9016306 DOI: 10.1177/002215549704500202]

33 **Tokunaga N**, Nagaya N, Shirai M, Tanaka E, Ishibashi-Ueda H, Harada-Shiba M, Kanda M, Ito T, Shimizu W, Tabata Y, Uematsu M, Nishigami K, Sano S, Kangawa K, Mori H. Adrenomedullin gene transfer induces therapeutic angiogenesis in a rabbit model of chronic hind limb ischemia: benefits of a novel nonviral vector, gelatin. *Circulation* 2004; **109**: 526-531 [PMID: 14732745 DOI: 10.1161/01.CIR.0000109700.81266.32]

34 **Vadivel A**, Abozaid S, van Haaften T, Sawicka M, Eaton F, Chen M, Thébaud B. Adrenomedullin promotes lung angiogenesis, alveolar development, and repair. *Am J Respir Cell Mol Biol* 2010; **43**: 152-160 [PMID: 19738161 DOI: 10.1165/rcmb.2009-0004OC]

35 **Murakami S**, Nagaya N, Itoh T, Iwase T, Fujisato T, Nishioka K, Hamada K, Kangawa K, Kimura H. Adrenomedullin regenerates alveoli and vasculature in elastase-induced pulmonary emphysema in mice. *Am J Respir Crit Care Med* 2005; **172**: 581-589 [PMID: 15947283 DOI: 10.1164/rccm.200409-1280OC]

36 **Nagaya N**, Nishikimi T, Uematsu M, Satoh T, Oya H, Kyotani S, Sakamaki F, Ueno K, Nakanishi N, Miyatake K, Kangawa K. Haemodynamic and hormonal effects of adrenomedullin in patients with pulmonary hypertension. *Heart* 2000; **84**: 653-658 [PMID: 11083748 DOI: 10.1136/heart.84.6.653]

37 **O'Callaghan DS**, Gaine SP. Combination therapy and new types of agents for pulmonary arterial hypertension. *Clin Chest Med* 2007; **28**: 169-185, ix [PMID: 17338934]

38 **Nakamura T**, Nawa K, Ichihara A. Partial purification and characterization of hepatocyte growth factor from serum of hepatectomized rats. *Biochem Biophys Res Commun* 1984; **122**: 1450-1459 [PMID: 6477569 DOI: 10.1016/0006-291X(84)91253-1]

39 **Mason RJ**, Leslie CC, McCormick-Shannon K, Deterding RR, Nakamura T, Rubin JS, Shannon JM. Hepatocyte growth factor is a growth factor for rat alveolar type II cells. *Am J Respir Cell Mol Biol* 1994; **11**: 561-567 [PMID: 7524567 DOI: 10.1165/ajrcmb.11.5.7524567]

40 **Panos RJ**, Patel R, Bak PM. Intratracheal administration of hepatocyte growth factor/scatter factor stimulates rat alveolar type II cell proliferation in vivo. *Am J Respir Cell Mol Biol* 1996; **15**: 574-581 [PMID: 8918364 DOI: 10.1165/ajrcmb.15.5.8918364]

41 **Hegab AE**, Kubo H, Yamaya M, Asada M, He M, Fujino N, Mizuno S, Nakamura T. Intranasal HGF administration ameliorates the physiologic and morphologic changes in lung emphysema. *Mol Ther* 2008; **16**: 1417-1426 [PMID: 18560414 DOI: 10.1038/mt.2008.137]

42 **Fortunato G**, Vidal DT, Klein W, Neto A, Angrizani A, Vasconcelos JF, Kaneto C, Souza BS, Ribeiro-dos-Santos R, Soares MB, Macambira SG. Recovery of pulmonary structure and exercise capacity by treatment with granulocyte-colony stimulating factor (G-CSF) in a mouse model of emphysema. *Pulm Pharmacol Ther* 2014; **27**: 144-149 [PMID: 23603459 DOI: 10.1016/j.pupt.2013.04.003]

43 **Maden M**. Retinoids have differing efficacies on alveolar regeneration in a dexamethasone-treated mouse. *Am J Respir Cell Mol Biol* 2006; **35**: 260-267 [PMID: 16574940 DOI: 10.1165/rcmb.2006-0029OC]

44 **Plantier L**, Marchand-Adam S, Antico Arciuch VG, Boyer L, De Coster C, Marchal J, Bachoual R, Mailleux A, Boczkowski J, Crestani B. Keratinocyte growth factor protects against elastase-induced pulmonary emphysema in mice. *Am J Physiol Lung Cell Mol Physiol* 2007; **293**: L1230-L1239 [PMID: 17766584 DOI: 10.1152/ajplung.00460.2006]

45 **Takahashi S**, Nakamura H, Seki M, Shiraishi Y, Yamamoto M, Furuuchi M, Nakajima T, Tsujimura S, Shirahata T, Nakamura M, Minematsu N, Yamasaki M, Tateno H, Ishizaka A. Reversal of elastase-induced pulmonary emphysema and promotion of alveolar epithelial cell proliferation by simvastatin in mice. *Am J Physiol Lung Cell Mol Physiol* 2008; **294**: L882-L890 [PMID: 18310229 DOI: 10.1152/ajplung.00238.2007]

46 **Criner GJ**, Connett JE, Aaron SD, Albert RK, Bailey WC, Casaburi R, Cooper JA, Curtis JL, Dransfield MT, Han MK, Make B, Marchetti N, Martinez FJ, Niewoehner DE, Scanlon PD, Sciurba FC, Scharf SM, Sin DD, Voelker H, Washko GR, Woodruff PG, Lazarus SC. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med* 2014; **370**: 2201-2210 [PMID: 24836125 DOI: 10.1056/NEJMoa1403086]

47 **Roszell B**, Mondrinos MJ, Seaton A, Simons DM, Koutzaki SH, Fong GH, Lelkes PI, Finck CM. Efficient derivation of alveolar type II cells from embryonic stem cells for in vivo application. *Tissue Eng Part A* 2009; **15**: 3351-3365 [PMID: 19388834 DOI: 10.1089/ten.TEA.2008.0664]

48 **Wang D**, Haviland DL, Burns AR, Zsigmond E, Wetsel RA. A pure population of lung alveolar epithelial type II cells derived from human embryonic stem cells. *Proc Natl Acad Sci U S A* 2007; **104**: 4449-4454 [PMID: 17360544 DOI: 10.1073/pnas.0700052104]

49 **Rankin S**. Mesenchymal stem cells. *Thorax* 2012; **67**: 565-566 [PMID: 22555276 DOI: 10.1136/thoraxjnl-2012-201923]

50 **Ishizawa K**, Kubo H, Yamada M, Kobayashi S, Numasaki M, Ueda S, Suzuki T, Sasaki H. Bone marrow-derived cells contribute to lung regeneration after elastase-induced pulmonary emphysema. *FEBS Lett* 2004; **556**: 249-252 [PMID: 14706858 DOI: 10.1016/S0014-5793(03)01399-1]

51 **Rojas M**, Xu J, Woods CR, Mora AL, Spears W, Roman J, Brigham KL. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. *Am J Respir Cell Mol Biol* 2005; **33**: 145-152 [PMID: 15891110 DOI: 10.1165/rcmb.2004-0330OC]

52 **Aliotta JM**, Keaney P, Passero M, Dooner MS, Pimentel J, Greer D, Demers D, Foster B, Peterson A, Dooner G, Theise ND, Abedi M, Colvin GA, Quesenberry PJ. Bone marrow production of lung cells: the impact of G-CSF, cardiotoxin, graded doses of irradiation, and subpopulation phenotype. *Exp Hematol* 2006; **34**: 230-241 [PMID: 16459191 DOI: 10.1016/j.exphem.2005.11.007]

53 **Carraro G**, Perin L, Sedrakyan S, Giuliani S, Tiozzo C, Lee J, Turcatel G, De Langhe SP, Driscoll B, Bellusci S, Minoo P, Atala A, De Filippo RE, Warburton D. Human amniotic fluid stem cells can integrate and differentiate into epithelial lung lineages. *Stem Cells* 2008; **26**: 2902-2911 [PMID: 18719226 DOI: 10.1634/stemcells.2008-0090]

54 **Chang JC**, Summer R, Sun X, Fitzsimmons K, Fine A. Evidence that bone marrow cells do not contribute to the alveolar epithelium. *Am J Respir Cell Mol Biol* 2005; **33**: 335-342 [PMID: 15961725 DOI: 10.1165/rcmb.2005-0129OC]

55 **Kotton DN**, Fabian AJ, Mulligan RC. Failure of bone marrow to reconstitute lung epithelium. *Am J Respir Cell Mol Biol* 2005; **33**: 328-334 [PMID: 15961722 DOI: 10.1165/rcmb.2005-0175RC]

56 **Macchiarini P**, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA, Dodson A, Martorell J, Bellini S, Parnigotto PP, Dickinson SC, Hollander AP, Mantero S, Conconi MT, Birchall MA. Clinical transplantation of a tissue-engineered airway. *Lancet* 2008; **372**: 2023-2030 [PMID: 19022496 DOI: 10.1016/S0140-6736(08)61598-6]

57 **Weiss DJ**, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebo-controlled, randomized trial of mesenchymal stem cells in COPD. *Chest* 2013; **143**: 1590-1598 [PMID: 23172272 DOI: 10.1378/chest.12-2094]

58 **Badylak SF**, Weiss DJ, Caplan A, Macchiarini P. Engineered whole organs and complex tissues. *Lancet* 2012; **379**: 943-952 [PMID: 22405797 DOI: 10.1016/S0140-6736(12)60073-7]

59 **Yokohori N**, Aoshiba K, Nagai A. Increased levels of cell death and proliferation in alveolar wall cells in patients with pulmonary emphysema. *Chest* 2004; **125**: 626-632 [PMID: 14769747 DOI: 10.1378/chest.125.2.626]

60 **Tsuji T**, Aoshiba K, Nagai A. Alveolar cell senescence in patients with pulmonary emphysema. *Am J Respir Crit Care Med* 2006; **174**: 886-893 [PMID: 16888288 DOI: 10.1164/rccm.200509-1374OC]

61 **Serrano-Mollar A**, Nacher M, Gay-Jordi G, Closa D, Xaubet A, Bulbena O. Intratracheal transplantation of alveolar type II cells reverses bleomycin-induced lung fibrosis. *Am J Respir Crit Care Med* 2007; **176**: 1261-1268 [PMID: 17641155 DOI: 10.1164/rccm.200610-1491OC]

62 **Fujino N**, Kubo H, Suzuki T, Ota C, Hegab AE, He M, Suzuki S, Suzuki T, Yamada M, Kondo T, Kato H, Yamaya M. Isolation of alveolar epithelial type II progenitor cells from adult human lungs. *Lab Invest* 2011; **91**: 363-378 [PMID: 21079581 DOI: 10.1038/labinvest.2010.187]

63 **Fadini GP**, Avogaro A, Ferraccioli G, Agostini C. Endothelial progenitors in pulmonary hypertension: new pathophysiology and therapeutic implications. *Eur Respir J* 2010; **35**: 418-425 [PMID: 20123847 DOI: 10.1183/09031936.00112809]

64 **Fadini GP**, Schiavon M, Cantini M, Baesso I, Facco M, Miorin M, Tassinato M, de Kreutzenberg SV, Avogaro A, Agostini C. Circulating progenitor cells are reduced in patients with severe lung disease. *Stem Cells* 2006; **24**: 1806-1813 [PMID: 16601079 DOI: 10.1634/stemcells.2005-0440]

65 **Takahashi T**, Suzuki S, Kubo H, Yamaya M, Kurosawa S, Kato M. Impaired endothelial progenitor cell mobilization and colony-forming capacity in chronic obstructive pulmonary disease. *Respirology* 2011; **16**: 680-687 [PMID: 21355963 DOI: 10.1111/j.1440-1843.2011.01959.x]

66 **Daly AB**, Wallis JM, Borg ZD, Bonvillain RW, Deng B, Ballif BA, Jaworski DM, Allen GB, Weiss DJ. Initial binding and recellularization of decellularized mouse lung scaffolds with bone marrow-derived mesenchymal stromal cells. *Tissue Eng Part A* 2012; **18**: 1-16 [PMID: 21756220 DOI: 10.1089/ten.TEA.2011.0301]

67 **Price AP**, England KA, Matson AM, Blazar BR, Panoskaltsis-Mortari A. Development of a decellularized lung bioreactor system for bioengineering the lung: the matrix reloaded. *Tissue Eng Part A* 2010; **16**: 2581-2591 [PMID: 20297903 DOI: 10.1089/ten.TEA.2009.0659]

**P-Reviewer:** Abdelmobdy Abdelrahim ME, Boots R, Pereira-Vega A

 **S-Editor:** Tian YL **L-Editor: E-Editor:**

**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.

