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Advances in pulmonary therapy and drug development: Lung tissue engineering to lung-on-a-chip

Ali Doryab [a,c], Ghassem Amoabediny [b,c,*], Amir Salehi-Najafabadi [c,d]

[a] Department of Life Science Engineering, Faculty of New Sciences and Technologies, University of Tehran, P.O. Box 14395-1561, Tehran, Iran
[b] Department of Chemical Engineering, Faculty of Engineering, University of Tehran, P.O. Box 11155-4563, Tehran, Iran
[c] Research Center for New Technologies in Life Science Engineering, University of Tehran, P.O. Box 63894-14179, Tehran, Iran
[d] Department of Microbiology, School of Biology, College of Science, University of Tehran, P.O. Box 11155-4563, Tehran, Iran

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ABSTRACT

Lung disease is one of the major causes of death, and the rate of pulmonary diseases has been increasing for decades. Although lung transplantation is the only treatment for majority of patients, this method has been limited due to lack of donors. Therefore, recently, attentions have increased to some new strategies with the aid of tissue engineering and microfluidics techniques not only for the functional analysis, but also for drug screening. In fact, in tissue engineering, the engineered tissue is able to grow by using the patient's own cells without intervention in the immune system. On the other hand, microfluidics devices are applied in order to evaluate drug screenings, function analysis and toxicity. This article reviews new advances in lung tissue engineering and lung-on-a-chip. Furthermore, future directions, difficulties and drawbacks of pulmonary therapy in these areas are discussed.
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Contents

1. Introduction

In the human body, the lung is an important respiratory organ and transporting oxygen from air into bloodstream is its main duty. Therefore as a vital organ, pulmonary diseases have also become one of the leading causes of death. Lung transplantation is the only treatment for them which is limited due to the lack of donors. Although the average waiting time in recent years has been declining, the annual lung transplantation is over 3700 (Yusen et al., 2014). Moreover, lung transplantation cannot be performed for patients whose disease is in severe condition, such as active hepatitis B, hepatitis C, or HIV (Kotloff and Thabut, 2011; Kotloff, 2013). Lung transplantation has also several risks including blood clots, infections, diabetes, and rejection of new lung (Ghanei et al., 2012; Kreider et al., 2011). Likewise, Chronic Obstructive Pulmonary Disease (COPD) is one of the most common lung diseases and over 3 million people die annually because of COPD (Lopez et al., 2006). In addition, according to conducted surveys, the burden of COPD is in the fifth rank and will be the third leading cause of death in 2020 (Cazzola et al., 2014; Mannino et al., 2002). Hence, investigations have been focused on other methods including lung tissue

* Corresponding author at: Department of Chemical Engineering, School of Engineering, University of Tehran, P.O. Box 11365-4563, Tehran, Iran.
E-mail address: amoabediny@ut.ac.ir (G. Amoabediny).

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engineering (LTE) that the tissue is able to grow by using the patient's own cells in which suppressing the immune system is not required (Reichenspurner, 2005; Yusen et al., 2014).

To improve the function of LTE, some methods including 3D culture on natural or synthetic-based scaffolds have been performed (Marelli-Berg et al., 2000; Rice et al., 2002; Vertrees et al., 2008). Lung tissue has sophisticated matrix to provide its main function, gas exchange or mechanical properties and growth of endothelial, epithelial and mesenchymal cells (Ott et al., 2010; Petersen et al., 2010). Therefore, to obtain these criteria and overcome difficulties of scaffold preparation, the process of recellularization of acellular natural tissue scaffolds is used (Lwebuga-Mukasa et al., 1986). This method is based on decellularization of the native lung as a suitable bio-scaffold. As a matter of fact, cell contents and DNA of the organ remain and consequently the 3D structure of the matrix is retained. Immediately afterwards, by recellularization, suitable cell sources are cultured on lung matrix. Recent attempts have been tried to improve efficacy of the whole procedure (Bonenfant et al., 2013; Bonenfanta et al., 2013; Booth et al., 2012; Cortiella et al., 2010; Crabbé et al., 2015; Jensen et al., 2012; Nakayama et al., 2013; O'Neill et al., 2013; Price et al., 2010; Shamis et al., 2011; Wallis et al., 2012). To create better qualified conditions and increase the efficacy of culturing, bioreactors are necessary. As a result, studies on lung tissue engineering lead outstanding progresses in order to treatlung injury and diseases. Additionally, it provides appropriate substrate to improve drug screening on experimental animal models.

On the other hand, advancements in research led to use the benefit of other techniques such as microfluidics in order to examine drug screenings, function analysis and toxicity. Several "organ-on-a-chip" devices have already been made (Esch et al., 2015; Huh et al., 2012, 2013; Kimura et al., 2014; Long et al., 2012; Xu et al., 2013). The Wyss Institute at Harvard, for instance, have fabricated a "lung-on-a-chip", which is mainly made of microfluidic channels, with a porous PDMS membrane on which alveolar epithelial and vascular endothelial cells are grown on either side of the membrane. Research on lung-on-a-chip indeed provides biomimetic microsystems that assist to assess the fundamental function of the lung especially alveolar-capillary interface. In addition, in drug studies and toxicity, 2D and 3D common cell culture methods as well as animal studies are usually time-consuming, costly and inefficient; therefore, these complex micro-devices are capable to investigate nano-toxicity studies, as an alternative method for animal models. Although lung-on-a-chip is a useful strategy to cover the drawbacks of previous investigations, it has its own specific challenges that should be considered.

This article reviews recent investigations on LTE approach and also advances on lung-on-a-chip. Furthermore, future directions of lung studies including main challenges and drawbacks are also described particularly.

2. Lung tissue engineering

2.1. Synthetic scaffolds

Scaffolds create suitable substrate for cells to generate a tissue or organ and consequently they are the opening stage for majority of tissue engineering studies (Amoabediny et al., 2011). In fact, many investigations try to find suitable scaffold using various methods. Investigations on synthetic-based scaffolds initially were performed by using biopolymer scaffolds.

The first study was reported by Douglas et al. to culture rat fetal lung cells on natural collagen matrix (Douglas et al., 1976). The porous scaffold was then obtained by freeze-drying method which comprises of collagen type I and chondroitin-6-sulfate and it was shown that alveolar network structures can be formed (Chen et al., 2005). In addition, several works on hydrogel and matrigel have indicated the generation of epithelial and endothelial structures. Recent studies of in vitro culturing of mouse pulmonary stem cells on gelatin scaffolds have shown that the alveolar-like structures and the alveolar pneumocytes have formed (Table 1).

In addition to studies on natural based scaffolds, as an appropriate cultivation substrate for pulmonary cell growth, other investigations focused on artificial or synthetic based (polymeric) scaffolds (Table 2).

Culture of murine and human lung epithelial cells on Poly (DL-lactic acid) (PDLLA) scaffolds have been studied by Lin et al. The results showed that PDLLA is non-toxic for pneumocytes and is effective for lung epithelial cell growth (Lin et al., 2010). Other investigations on Polyglycolic Acid (PGA) scaffold showed that vascular and alveolar regeneration are supported by PGA scaffold (Cortiella et al., 2006). Also, culture of rat alveolar cells on synthetic scaffold of poly-2-hydroxyethyl methacrylate (poly HEMA) indicated the adhesion and growth of cells. Regenerative medicine studies in the respiratory system including trachea, bronchus and the distal parenchyma have shown that generating a piece of lung tissue such as tissue-engineered trachea was the main result of these studies (Nichols and Cortiella, 2008) (Table 3) (Fig. 1e-f).

2.2. Decellularized lung scaffold

Several strategies have been reported to establish the airway and vascular structures which are extremely important for lung function. However, synthetic scaffolds for lung tissue engineering were not able to create a network branching or produce Extra Cellular Matrix (ECM)

Table 1
Investigations on natural-derived scaffolds to aid lung regeneration.

Scaffold(s)	Cell population(s)	Differentiated phenotype/other descriptions	Reference
Collagen gel matrix	Rat alveolar type II epithelial cells	Growth of type II epithelial cells and formation of alveolar-like structure in the collagen scaffold	Sugihara et al. (1993)
Gelfoam	Rat fetal lung cells	Survival and proliferation of pre-labeled fetal lung cells maintained for up to 35 days	Andrade et al. (2007)
Gelatin	Mouse pulmonary stem/progenitor cells	Formation of alveolar pneumocytes and alveolar-like structure	Cortiella et al., (2006)
Collagen gels	Mouse fetal pulmonary cells	Supported extensive epithelial budding and sacculation and robust endothelial network formation	Ling et al. (2014)
Matrigel, PLGA, PLLA	Mouse fetal pulmonary cells	Supported the formation of lumen-containing spherical cystic epithelial structures	Mondrinos et al. (2006)
Matrigel	Mouse fetal pulmonary cells	Facilitated the interfacing between epithelial alveolar forming units and capillary-like tubes with continuous lumens	Mondrinos et al. (2007)
Collagen matrix	Rat fetal lung cells	Drove formation of alveolar-like cystic structures with extended maintenance of epithelial cell differentiation in vitro	Douglas et al. (1976)
Porous collagen type I-chondroitin-6-sulfate	Rat fetal lung cells	Supported the formation of alveolar-like structures	Chen et al. (2005)

Matrigel: a compliant natural ECM hydrogel, Gelfoam: a gelatin-based porous sponge, PLGA: poly-lactic-co-glycolic acid, PLLA: poly-L-lactic-acid.

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Table 2
Investigations on synthetic based scaffolds to support lung regeneration.

Scaffold(s)	Cell population(s)	Differentiated phenotype/other descriptions	Reference
PGA and F-127 hydrogels	Ovine somatic lung progenitor cells	Lung progenitor cells proliferated on PGA scaffolds in vitro but the scaffolds induced a foreign body response in vivo	Cortiella et al. (2006)
PDLLA	Murine lung epithelial cells	PDLLA is not only nontoxic to pneumocytes but also it actively supports their growth	Lin et al. (2006)
PDLLA	Human pulmonary epithelial cells	PDLLA affects significantly the behavior of pulmonary epithelial cells growing	Lin et al. (2006)
PGA sheets	Rat adipose tissue–derived stromal cells	Both alveolar and vascular regeneration were significantly accelerated	Shigemura et al. (2006)
Poly HEMA	Rat alveolar cells	The polymer affects the alveolar cell adhesion and growth	Radhakumary et al. (2011)

PDLLA: poly-DL-lactic acid, PGA: polyglycolic acid, Poly HEMA: poly (2 hydroxyethylmethacrylate).

components which lie between the capillary endothelium and the alveolar epithelium. In addition, native lung ECM contains a variety of proteins such as collagen, elastin, and fibronectin which do not exist in synthetic materials to provide structural and biochemical supports to the supporting cells. As a result, decellularized lung scaffolds were used to prevail the challenges of synthetic-based scaffolds (Petersen et al., 2010). Acellular scaffolds can be provided by decellularization process in which all the cellular and nuclear materials are removed and key components of ECM are preserved (Ott et al., 2010). In fact, after obtaining suitable scaffolds, cell repopulation are carried out by recellularization. First attempt to evaluate lung regeneration using this method was reported by Lwebuga-Mukasa et al. (1986). The investigations on different animal species with clinical application purposes were also performed and engineered-lung tissue was implanted and functional performances of lung grafts were evaluated. In fact, not only can engineered-lung tissue transfer nutrients, but with the aid of respiratory movement or ventilation it can also lead to differentiate of pneumocyte type I and pneumocyte type II (Inanlou and Kablar, 2005; Inanlou et al., 2005). In addition, Price et al. developed the bioreactor system to reseed lung acellular matrix (Price et al., 2010). Histochemical analysis of lung matrices, which have been incubated for 7 days, showed that the entire original structures were intact and collagen was maintained at normal levels. The amounts of elastin, laminin and Glycosaminoglycans (GAGs) compare with ECM of native lungs were at a lower level and fetal type II alveolar epithelial cells are able to culture. This study indicated that the natural 3D matrix could be a good substrate for culturing stem cells to regenerate tissue-engineered lung. Reseeding process for one week showed that cell phenotype and scaffold integrity have been preserved. The results also showed that perfusion has significant effects on pulmonary cell survival and cell differentiation (Petersen et al., 2011). However, vascular perfusion alone is not sufficient to culture the whole lung and causes loss of cell differentiation, which leads to increased rates of apoptosis. In addition, air ventilation has destructive impact on airway epithelium and causes decrease of nutrient delivery. Therefore, ventilation by using media was applied to eliminate this problem.

Although prior investigations have indicated that recellularization of lung tissues in vitro is feasible, it has its own drawbacks. However, recent investigations indicate promising advances in the area of LTE (Table 4). For example, the first attempt for applying whole acellular lung tissue showed that decellularized matrix permits better differentiation of embryonic stem cells (Cortiella et al., 2010). In addition to its potential application, to promote the sustainability of implantation of tissue-engineered lungs, suitable cell sources were reseeded and the results show the duration of implantation stability increased to 14 days (Song et al., 2011, 2013). Furthermore, application of bioreactors plays the main role in reseeding investigations. For instance, a novel rotating bioreactor that provides air-liquid interface (ALI) system and mimics in vivo respiratory conditions was used to differentiate human induced pluripotent stem cells derived type II pneumocytes (iPSC-ATII) and human type II pneumocytes (hATII) toward a type I phenotype. In fact, the results of this work indicates the effectiveness of the ALI bioreactor (Fig. 1g-h). What's more, this study demonstrated a strategy for large-scale production of alveolar epithelium for tissue engineering and drug screening (Ghaedi et al., 2014). On the other hand, to overcome the scaling up problems, some studies were performed to develop the total process (Fig. 1a-c) (Bonvillain et al., 2013). Acellular scaffolds undergo substantial matrix damage due to the harsh conditions of decellularization such as detergents. Balestrini et al., developed a new decellularization technique using a combination of Triton X-100 and sodium deoxycholate (SDC) at low concentrations to overcome this challenge (Balestrini et al., 2015). Hill et al., have also developed a targeted proteomics method to characterize ECM proteins from tissue. This procedure will assist the next generation of engineered organs by creating a molecular readout (Hill et al., 2015). Consequently, some major challenges during recellularization including nutrients transferring,

Table 3
Summary of investigations on tissue-engineered trachea and bronchus.

Tissue or section	Main compositions	Species	Key results after implantation	Reference
Left main bronchus	Polypropylene mesh tube, conjugation of collagen extracted from porcine skin	Dog	1. Stable remaining of prosthesis 2. No observation of adverse effects such as infection, sputum retention, or dehiscence	Sato et al. (2008)
Trachea	Collagen sponge scaffold, adipose-derived stem cells	Rat	A pseudostratified columnar epithelium with well-differentiated ciliated and goblet cells and neovascularization	Suzuki et al. (2008)
Trachea	Marlex mesh tube, reinforced with polypropylene threads, conjugation of collagen sponge	Dog	1. No airway obstruction 2. Covering of endolaryngeal and endotracheal lumen by ciliated epithelium 3. Supporting of framework by regenerated tissue	Omori et al. (2008)
Left main bronchus	Human donor trachea, epithelial cells and mesenchymal stem cell derived chondrocytes	Human	1. Normal mechanical properties 2. No anti-donor antibodies were seen 3. No immunosuppressive drugs were needed	Macchiarini et al. (2008), Otti et al. (2014)
Bronchioles	Human bronchioles, fibroblasts, airway smooth muscle cells, small airway epithelial cells and extracellular matrices	Human	N/A (Bronchiole phenotypic stability was verified by immunohistochemistry. Protein expression verified a change in phenotype after the initial fabrication stage)	Miller et al. (2010)

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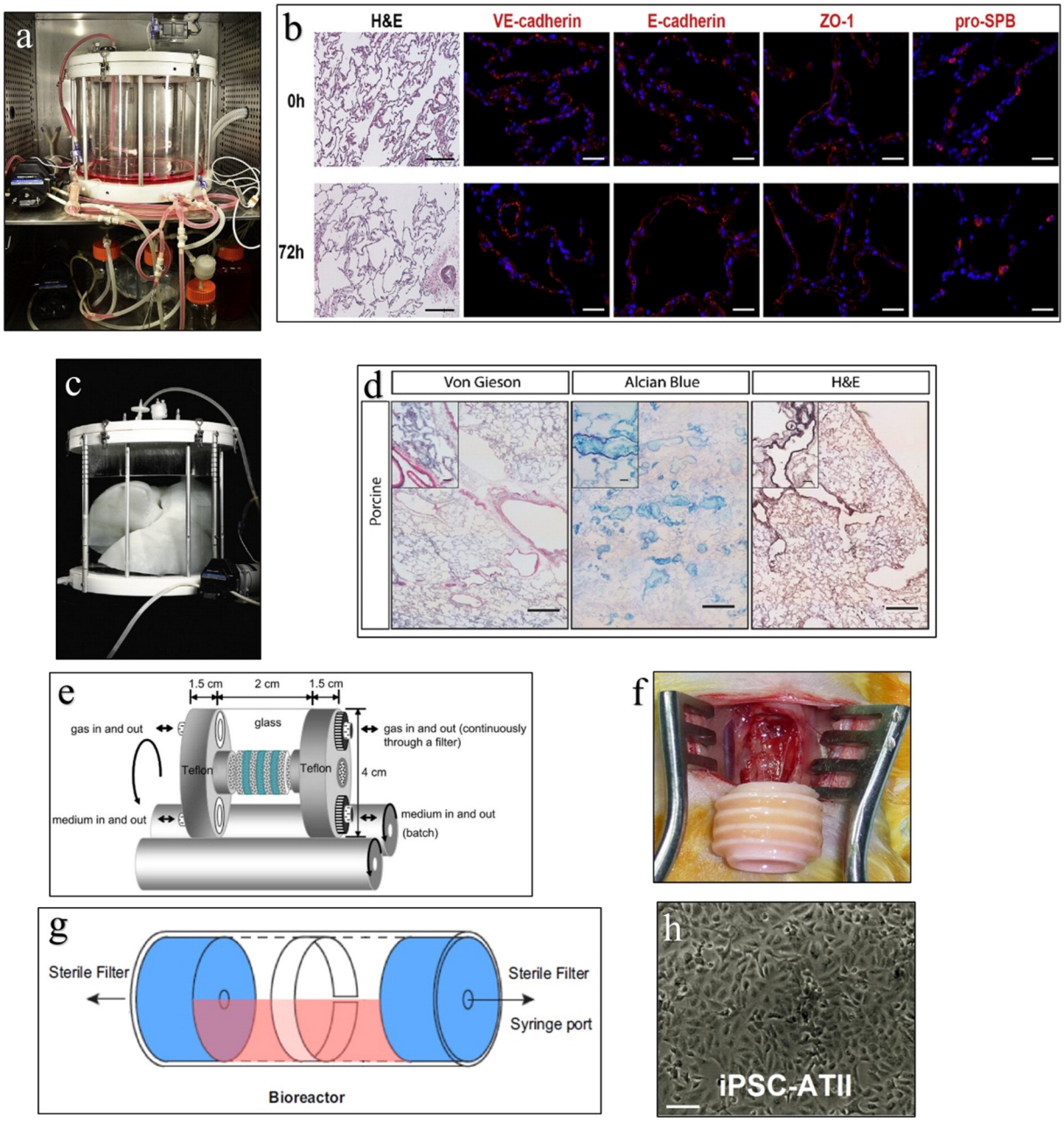

Fig. 1. Some of the bioreactor applications in respiratory tissue engineering. (a–b) Photograph of a clinical-scale bioreactor for long-term isolated lung culture setup in an incubator (a) and histological and immunofluorescent analysis of human lung tissue before (0 h) and after (72 h) long-term lung culture (b). Hematoxylin and eosin staining (H&E, scale bar, 250 mm). VE-cadherin, E-cadherin, ZO-1, and pro-SPB (red, nuclei blue, scale bar 50 mm) reproduced with permission (Charest et al., 2015). (c–d) A custom-designed decellularization chamber used for cannulation of lungs through the pulmonary artery (c) and matrix analysis of porcine decellularized lung tissue. (Left) Elastin (blue-black) by Verhoeff-Van Gieson across species. (Middle) Preservation of glycosaminoglycans (blue) by Alcian blue, and (right) loss of cellular components in decellularized porcine lung tissue, as visualized by hematoxylin and eosin (H&E). Main scale bar is 200 μm, inset scale bar is 20 μm (d) reproduced with permission (Gilpin et al., 2014). (e–f) A schematic diagram of a scaffold-bioreactor system for a tissue-engineered trachea (e) and implantation of the PCL–collagen construct as a tracheal graft in rabbits (f) reproduced with permission (Lin et al., 2009). (g–h) Schematic figure of the rotating bioreactor used for differentiation of human induced pluripotent stem cells to alveolar epithelial cells (g) and phase-contrast images of differentiated cells at day 22,which are termed ATII cells (h) reproduced with permission (Ghaedi et al., 2014).(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

mimicking the native physiological conditions, long-term culturing and scaling up were modified to obtain functional tissue-engineered lung for in vivo implantation.

2.3. Human studies

A tissue-engineered airway was successfully implanted and the results have shown that acellular scaffold is a suitable matrix for lung regeneration. Tissue-engineered lung for in vivo conditions (up to 6 h) also showed that the applied procedure could be used for clinical applications in human. Their proposed method was implemented in other animal species including pig and sheep; hence, it demonstrated that despite the presence of type II pneumocyte, alveoli had not been formed well (Macchiarini et al., 2008; Ott et al., 2010).

To scale-up the process, hence, culture of macaque lung under tension and mechanical stress by negative pressure ventilation and perfusion have been implemented (Bonvillain et al., 2013). Mesenchymal stromal cells derived from Human Bone Marrow derived Mesenchymal Stem Cells (hBM-MSCs) and Human Adipose Tissue derived MSCs (hAT-MSCs) were cultured on acellular scaffold under appropriate culture conditions and it has been shown that these cells were suitable for recellularization of decellularized lung scaffolds (Mendez et al., 2014).

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Table 4
Summary of paradigm investigations on acellular lung matrix scaffolds to aid or support lung regeneration.

Scaffolds/Species	Cell population(s)	Differentiated phenotype/prominent results	Reference
Mouse	Mouse FLCs	The analysis showed that the lung matrix was intact	Price et al. (2010)
Rat	A549 cells, rat FLCs and HUVECs	Epithelial and endothelial cells were cultured on the scaffold. After transplantation of tissue-engineered lung in the orthotropic position, gas exchange was performed in vivo condition (up to 6 h)	Ott et al. (2010)
Rat	A549 cells, HUVECs, rat NLCs and rat LVECs	Effects of pulmonary perfusion and ventilation on cell viability, survival and differentiation in the bioreactor	Petersen et al. (2010)
Rat	Mouse ESCs	The first attempt to produce and apply whole lung tissue in order to growth of MESCs	Cortiella et al. (2010)
Rat	Rat FLCs and HUVECs	promotion the in vivo transplantation sustainability time up to 14 days	Song et al. (2011)
Rhesus macaque	Rhesus BM-MSCs and A-MSCs	Culture of MSCs derived from bone marrow cells on acellular lung scaffold	Bonvillain et al. (2012)
Mouse	Mouse BM-MSCs and C10 epithelial cells	Effect of storage time and tissue sterilizing on decellularization and recellularization	Bonenfanta et al. (2013)
Human and pig	Mouse ESCs, human FLCs, pig BM-MSCs and human AETII	The first attempt to produce a large lung scaffold	Nichols et al. (2013)
Rat	Human BM-MSCs and A-MSCs	Differentiation of mesenchymal stromal cells derived from human bone marrow and human adipose tissue to epithelial phenotype of lung on acellular scaffold	Mendez et al. (2014)
Rat, human and pig	Human SAECs, human PECs and HUVECs	Lung decellularization in a large scale	Gilpin et al. (2014)
Pig	Human A549 cells	A new decellularization technique was described	Balestrini et al. (2015)

MSCs: mesenchymal stromal cells; FLCs: fetal lung cells; HUVECs: human umbilical vein endothelial cells; NLECs: neonatal lung epithelial cells; LVECs: lung vascular endothelial cells; ESCs: embryonic stem cells; BM-MSCs: bone marrow derived mesenchymal stromal cells; A-MSCs: adipose tissue derived mesenchymal stromal cells; AETII: alveolar epithelial type II cells; SAECs: small airway epithelial cells; PECs: pulmonary epithelial cells.

In addition, adherence, differentiation and proliferation of these cells demonstrated the capacities of these cells including the ability to differentiate into lung epithelial cells, high proliferation ability, availability and lack of immune system stimulation. Besides, large-scale decellularization has been examined to create a biocompatible scaffold for culturing Pulmonary Alveolar Epithelial Cells (PAECs) up to 96 h. Although the applied procedure creates an implantable lung which is able to exchange oxygen, some problems such as duration of sustainability, compliance and gas exchange reduction after 7 days should be addressed. Recently, recellularization protocol of whole acellular human pediatric lung scaffolds has been developed. Regeneration of vascular, respiratory epithelial and lung tissue and also alveolar–capillary junction formation have been shown in bioengineered pediatric lungs (Nichols et al., 2016). Although these results were promising, we concluded that these studies require more investigations to demonstrate the feasibility of producing bioengineered lungs for clinical use.

3. Lung-on-a-chip

The complex structure of the lung and challenges between humans and animal models lead the researcher to find appropriate method in order to recapitulate lung structure and function as the same as normal level. Organ-on-a-chip systems make bridge between microfluidic technology and living cells to investigate human physiology. This microdevice mimics the physiological and mechanical microenvironment of a native lung. As a matter of fact, organ-on-a-chip assists the researcher to study the main function of lung, pulmonary diseases and drug screening. These microfluidic devices are also able to develop controlled system for long-term differentiation of various kinds of cells (Table 5).

The lung-on-a-chip is modeled to study functions of lung by integrating epithelial and endothelial cells on two porous PDMS cell-culture chambers, coating it with ECM, which separated by a thin polyester membrane. In addition, this device is able to mimic the complex 3D structure, resembles the lung function and mechanical stress due to respiration. In fact, the alveolar-barrier microenvironment was produced to investigate air-interface responses or to epithelial capillary barrier as along functions on a lab. Physiological breathing movements and blood flow were also imitated by applying regularly repeated suction and the results were well-matched with normal levels. Furthermore, human lung responses to physiological inflammatory stimuli were evaluated. This system, consequently, introduced a low-cost screening platform in order to develop the findings of animal and clinical trials (Huh et al., 2010, 2013).

To manage multiple factors on a single platform, a microfluidic platform was provided which focus on long-term and stable culturing at an ALI. In fact, this system creates an air-interface together with microfluidic and cell seeding membrane. This proposed platform is also applied to determine the optimal growth conditions of various lung-specific cell types (Nalayanda et al., 2009, 2010).

The cyclic mechanical stress on epithelial barrier permeability was also applied to mimic the diaphragm in vivo. This intermitted stretch also influenced the metabolic activity and the cytokine secretion of primary human pulmonary alveolar epithelial cells. Furthermore, some efforts were performed to make a better handling and provide the same in vivo features and consequently examine human responses to toxicity and drugs. The lung alveolar barrier were reconstituted and 3D cyclic mechanical strains were done by a pneumatic part to mimic the diaphragm in vivo (Stucki et al., 2015). The most recent advance in this area indicates the “breathing lung-on-a-chip” microdevice which was used for studying the nontoxicity and human disease (Huh, 2015).

However, this microfluidic chip-based has many applications in evaluating drug screening. In this method, a disease model platform was developed to support individualized treatment. In fact, by mimicking the actual tumor microenvironment in vivo, lung cancer cells were cultured in a three-dimensional (3D) culturing system and after that they were treated with anti-cancer drugs to examine the effects of various types and doses of drugs (Xu et al., 2013).

Furthermore, some studies have been conducted to develop the integrated organ-on-a-chip that regenerates vital functions of living organs in a unit system (Table 6). Evaluation of multiple organ systems at single device led to understanding human physiology and pathology (Kimura et al., 2014; Zhang et al., 2009).

Compared to conventional models, the lung-on-a-chip provides a platform to investigate the complex effects (chemical, biological and mechanical), cell behaviors in vitro and drug screening (Wang et al., 2016). For example, a multichannel-dual-electric-field chip was reported to examine the effect of chemicals and electric-field at the same time on lung cancer cells (Hou et al., 2014). Furthermore, hybrid optimization of device geometry and flow rate using computational fluid dynamics (CFD) were applied for better mimicking in vivo lung functions (Long et al., 2012).

Although these results were promising, we concluded that the results were not adequate to produce a device to investigate human

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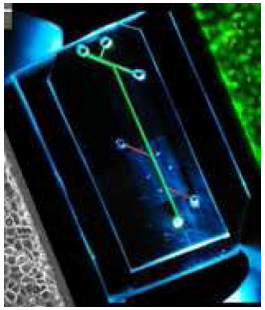
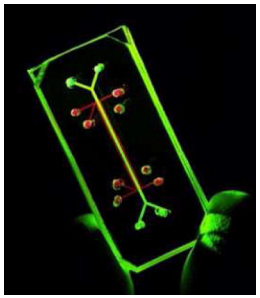
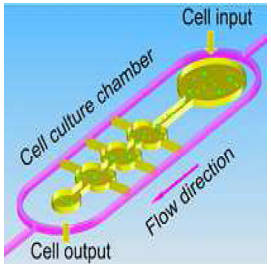
Table 5
Recent investigations on lung-on-a-chip.

Type of testing	Features	Lung-on-chip microfluidic device	Cell sources	Details	Reference
Disease model	Monitor epithelial small airway cell damage caused by liquid propagation Plug generator at the upper chamber to generate plug in the airway-like channel.		SAECs	The first chip to investigate mechanical injury of epithelial cells within the small airway system caused by liquid plug rupture.	(Huh et al., 2007) Reproduced with permission from (Tavana et al., 2011)
Function analysis/disease model	A model for function studies at an air-liquid interface		A549 alveolar epithelial cells	The chip focuses on long-term and stable culture at the ALI	(Nalayanda et al., 2009) (de Souza Carvalho et al., 2014) Reproduced with permission from (Nalayanda et al., 2010)
Function analysis/disease model	Mimic immune response to microbial infection in human alveoli. Relation between Nanoparticle effects on lung inflammatory and breath motion. Modeling nanoparticle transport from alveoli into the lung vasculature		NCI-H441 EGM-2MV	Increased production of surfactant by epithelial cells. Permeability measurement simultaneously with cyclic stretch and fluid shear stress to both sides. Investigate relation between nanoparticle effects on lung inflammatory and breathe motion. Can be a Human lung disease model on-chip that helps researchers reconstitute toxic side effects of IL-2.	Reproduced with permission (Huh et al., 2010) (Huh et al., 2011) (Huh et al., 2013) (Huh et al., 2012) (Huh, 2015)
Disease model	Anti-lung-cancer drug test chip Mimicking the actual tumor condition in vivo.		SPCA-1 and HFL1	Drug gradient generator for different drug concentration responses Winding channels to prevent backflow	Reproduced with permission (Xu et al., 2013)

SAECs: (primary human small airway epithelial cells), ALI: Air-Liquid Interface, IL-2: interleukin-2, SPCA-1: secretory pathway calcium ATPase 1 (cancer cells), HFL1: Human fetal lung fibroblast cells, 16HBE14o-: Human Bronchial epithelial cells, pHUVEC: Primary human umbilical vein endothelial cells, NCI-H441: human alveolar epithelial cell line, EGM-2MV: human lung microvascular endothelial cells.

Table 6
Some prominent integrated organ-on-a-chip.

Integrated organs	Features	Details	Reference
Liver, small intestine	-Based on physiological blood circulation and organ volume Stirrer-based -Micropumps connected to microchannels. -Drugs tested: EPI, CPT-11, CPA	Lung was adopted as a target organ for anti-cancer drugs.	Kimura et al. (2014)
Liver, kidney, fat	Gelatin microspheres used to control releases in chambers	As TGF-β1 could enhance the functions of A549 cell lines, it was introduced to the lung chamber in addition to common culture medium. Four inlets connected to a cell reservoir which includes a two way valve and a luer connection.	Zhang et al. (2009)

EPI: epirubicine, CPT-11: irinotecan, CPA: cyclophosphamide, TGF-β1: transforming growth factor, beta 1.

physiology. On the other hand, lung-on-a-chip device has some challenges. For example, PDMS is one of the main problems which has an adverse impact on efficacy and pharmacological activities (Berthier et al., 2012). Although surface modification methods such as chemical have been used to address this problem, absorbing small hydrophobic molecules by PDMS chips are still having trouble (Kuddannaya et al., 2013; van Midwoud et al., 2012). Moreover, human cell sources are another essential part in the development of organ-on-a-chip microdevice. Recently, human embryonic stem cells and induced pluripotent stem cells have been used as cell sources in different kinds of organ-on-a-chip (Park et al., 2015; van de Stolpe and den Toonder, 2013). Furthermore, microengineered platforms are needed to detect biological responses in organs-on-chips.

4. Future directions of lung studies

Lung tissue engineering (LTE) currently is the appropriate method as an alternative treatment for pulmonary disease. However, LTE has many drawbacks and further investigation requires overcoming the gaps of LTE. Since, lung tissue has complex structure; therefore, to achieve better matrix and overcome challenges in scaffold preparation, decellularized scaffold was suggested to use in re-seeding process (Lwebuga-Mukasa et al., 1986).

This method has several benefits and provides more precise results rather than other methods. Nevertheless, some disadvantages remain throughout the whole process of recellularization. In fact, selecting suitable cell sources, sterilization protocol of matrix, media and growth factors are the most problems. Furthermore, to obtain efficient lung engineered tissue, monitoring the reseeding, appropriate bioreactor and scaling up are the significant difficulties which should be studied in detail for future investigations.

Likewise, lung-on-a-chip that regenerates physiological responses the same as the normal level could influence on future lung investigations as replacements for animal tests in development of drug screening and toxicology. These micro-devices also provide online monitoring and analysis during various trends which are not feasible by other conventional methods. In addition to its benefits, some drawbacks have remained. First of all, although lung-on-a-chip provides suitable in vitro lung tissue model and is able to evaluate responses to pulmonary diseases, some complex pulmonary diseases are not able to reproduce in vitro. Furthermore, some mechanisms in lung damage and fibrosis are difficult to assess. Finally, since research on this microfluidic chips has been limited to short-term culture, therefore, these micro-devices should be developed to long-term cultivation. As a result, future attempts must be oriented to combine all of the above in order to obtain reliable model.

All in all, investigations on pulmonary therapy are in its infancy. Although, promising works have been performed in this area, further studies are required to find more information about critical points in engineered lung tissue. Accordingly, more accurate model which is able to mimic the native human lung should be fabricated.

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