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Research review paper

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

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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.

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

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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.