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Perspective

Chronic lung disease, lung regeneration and future therapeutic strategies

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Abstract

Chronic lung diseases have been recognized as one of the world's leading causes of death in recent decades. Lacking effective treatments brings the patients not only bad quality of life but also higher risk for lung cancer development. By increasing the understanding of deeper mechanism of how lung develops and regenerates, researchers now focus on studying lung regenerative medicine, aiming to apply different and more efficient therapies to treat chronic lung diseases. This review will provide a wide picture of both basic lung developmental, regeneration mechanism and different designed strategies for treating chronic lung diseases in the future decades.

Keywords: Chronic obstructive pulmonary disease; Lung developmental mechanism; Regeneration medicines

Introduction

Chronic degenerative lung diseases are recognized as untreatable pathological diseases, significantly affecting both life span and life quality of human-beings. Chronic obstructive pulmonary disease (COPD) presents a group of lung diseases which block the airflow and lead patients difficult to breathe, is predicted to be the third leading cause of death by the end of 2020s according to the World Health Organization. It is also widely established that patients with COPD are at increased risk for the development of primary lung cancer. Based on current medicine and technologies, the only treatment for COPD is lung transplantation, while there is always acute shortage of donor lungs. It has been reported that adult lung has the capacity for both regeneration and regrowth.[1,2] However, loss of alveolar units and the emerging of pulmonary fibrosis often trigger repeated episodes of injury, thus resulting in unceasing consumptions of endogenous lung repair capacity.[3] This makes the authentic therapeutic lung regeneration still a long-term goal. Recent emerging regenerative medicine has shed a light on the path for finding a new way to treat the COPD instead of seeking lung transplantations. Approaches include not only generating new lungs

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in vitro and replenishing exogenous stem cells to the damaged parts,[4] but also using pharmacologically selection for promoting the healthy cells survival other than damaged ones. All these methods are based on numerous basic researches focusing on lung developmental and regeneration pathways. Therefore, this review will mainly discuss the current and newest lung regrowth and developmental mechanism discovered, with the possibilities of serving future applications for the therapeutic lung regeneration.

Developmental mechanism of lung

The discussion of the lung regeneration mechanisms requires a thorough understanding of how lung generates during normal developmental process. The majority researches focusing on mammalian lung development are conducted by using mice models. With the effort of numerous studies, now we know that the mammalian lung development can be divided into three phases: (1) Specification of lung progenitors; (2) Branching morphogenesis; (3) Sacculation and alveolarization.[5]

The initiation of lung development is relied on the specification of lung endoderm which derives from the ventral side of anterior foregut endoderm (Fig. 1). The biomarker for this phase is the highly expressed NK2 homeobox 1 (Nkx2.1),[6] who is one of the developmental pioneer transcription factors family. Embryonic day 9 (E9.0) in mice is the approximate time for this event happening. Around embryonic day 9.5 (E9.5), a proximal-distal patterning of endoderm begins with the differential expression of sex determining region Y-Box 2 (Sox2). Then the Sox9 and inhibitor of differentiation 2 (Id2), which determine the most distal tips of branching epithelium, are proximally demarcated by the expression of Sox2. This is the signal of entering the step 2 phases. The cells that highly express the Sox9 and Id2 are multipotent before embryonic day 13.5 (E13.5), and will be restricted in the fate for generating alveolar type 1 and alveolar type 2 cells (AT1 and 2 cells) after E13.5.[7] This point is one of the important dates for various lung regeneration models, while the differentiation of the Sox9+, Id2+ cells contribute essentially for generating functional alveolar gas exchanging units. However, recent researches indicate that a bipotent progenitor may be responsible for the generation of lung alveolus, the detailed mechanism still is little understood.

Airway epithelial lineages are determined by the Sox2 progenitors, whereas other lineages are also produced during the Sox2 early endoderm differentiation, this majorly reflects the developmental process reaches phase 3. Tumor protein P63 (Trp63), keratin (Krt) and podoplanin (Pdpn) are the markers of basal cells, who generate multi-ciliated cells after airway injury from adult trachea.[8] Club cells in which secretoglobin family 1A member 1 (Scgb1a1) and cytochrome P450 family 2 subfamily F member 2 (Cyp2f2) are highly expressed, with the basal cells

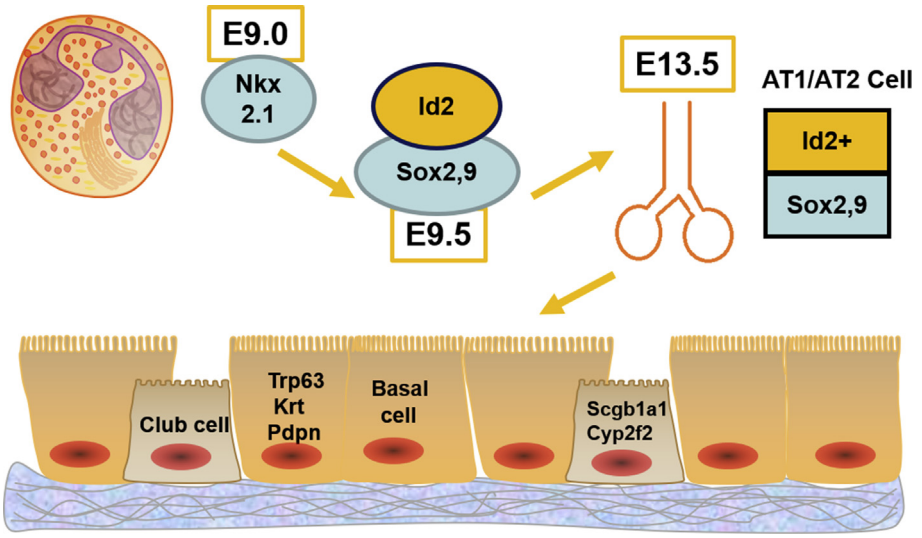

Fig. 1. E9.0- E13.5 mice embryonic specification of lung progenitors. Scheme for mice embryonic specification of lung progenitors, from E9.0-E13.5, a continuous process of different pioneer transcription factors that differentially expressed, leading to the formation of adult lungs. E9.0: embryonic day 9; Nkx2.1: NK2 homeobox 1; Id2: inhibitor of differentiation 2; E13.5: embryonic day 13.5; AT1/AT2 cell: alveolar type 1 and alveolar type 2 cell; Sox2,9: sex determining region Y-Box 2,9; E9.5: embryonic day 9.5; Trp63: tumor protein P63; Krt: keratin; Pdpn: podoplanin; Scgb1a1: secretoglobin family 1A member 1; Cyp2f2: cytochrome P450 family 2 subfamily F member 2.