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Review article

Developmental mechanisms and adult stem cells for therapeutic lung regeneration

Joo-Hyeon Lee[a,b,*], Emma L. Rawlins[c,d,**]

[a] Wellcome Trust/Medical Research Council Stem Cell Institute, University of Cambridge, Cambridge, UK
[b] Department of Physiology, Development and Neurobiology, University of Cambridge, Cambridge, UK
[c] Wellcome Trust/CRUK Gurdon Institute, University of Cambridge, UK
[d] Department of Pathology, University of Cambridge, Cambridge, UK

ABSTRACT

Chronic degenerative lung diseases are essentially untreatable pathological conditions. By contrast, the healthy lung has numerous mechanisms that allow for rapid repair and restoration of function following minor acute injuries. We discuss the normal endogenous processes of lung development, homeostatic maintenance and repair and consider the research strategies required for the development of methods for human therapeutic lung regeneration.

1. Introduction

One definition of regeneration is the ability of an organ to regrow a fully functional replacement following catastrophic loss; classical regenerative organs include newt limbs and zebrafish hearts. Lungs are slow-turnover organs that are highly quiescent at steady-state. However, the lung has a tremendous ability to repair epithelial damage following acute injury and contains multiple, highly plastic, stem cell populations. Following partial pneumonectomy (removal of one entire lung lobe) in a mouse the remaining lung lobes undergo compensatory growth to restore gas exchange capacity; meeting a functional definition of regeneration (Fehrenbach et al., 2008; Voswinckel et al., 2004; Young et al., 2015). In humans there is clinical evidence for adult lung regrowth following partial pneumonectomy, or severe flu infection (Butler et al., 2012; Toufen et al., 2011). In spite of this intrinsic ability to repair and regenerate, chronic degenerative lung disease in humans is an essentially untreatable condition, significantly affecting length, and quality, of life. The World Health Organisation predicts that Chronic Obstructive Lung Disease (COPD) will become the third leading cause of death worldwide by 2030. The only treatment for many end-stage chronic lung diseases is transplantation and there is an acute shortage of suitable donor lungs.

If the lung has a capacity for repair and regrowth, how is chronic lung disease such a problem? Current hypotheses suggest that COPD, in which alveolar units are often lost, and pulmonary fibrosis, in which alveoli are clogged with scar tissue, are the end result of repeated episodes of injury which have exhausted the lung's endogenous repair capacity; likely coupled to a sensitive genetic background (Gunther et al., 2012; Kheirallah et al., 2016). Therapeutic lung regeneration is therefore a long-term goal of many research programmes. Approaches for therapeutic lung regeneration include growing new lungs in vitro and the addition of exogenous stem cells to damaged lungs (Weiss, 2014). An alternative approach would be to pharmacologically manipulate surviving healthy cells to restore diseased lungs. Given the intricate and complex structure of the lung the concept of activating endogenous developmental, or repair, mechanisms is very attractive. We discuss our current understanding of the normal developmental/homeostatic and repair/regeneration mechanisms employed by the mammalian lung and consider the research strategies required to allow the manipulation of these processes for therapeutic regeneration.

2. Lung structure and organisation

The adult lung is composed of branching networks of epithelial tubes and blood vessels which meet at the alveoli. Air enters the nasal passages, passes down the trachea and successively finer branches of the conducting airways (bronchioles) until it reaches the alveolar network where gas exchange occurs (Fig. 1). The major airways are supported by C-shaped cartilage rings and smooth muscle and lined by a pseudostratified columnar epithelium consisting of basal, secretory (predominantly mucous-secreting goblet cells in human, but club cells in mice) and ciliated cells. Rarer chemosensory epithelial cells include

* Corresponding author at: Wellcome Trust/Medical Research Council Stem Cell Institute, University of Cambridge, Cambridge, UK
** Corresponding author at: Wellcome Trust/CRUK Gurdon Institute, University of Cambridge, Cambridge, UK
E-mail addresses: jhl62@cam.ac.uk (J.-H. Lee), e.rawlins@gurdon.cam.ac.uk (E.L. Rawlins).

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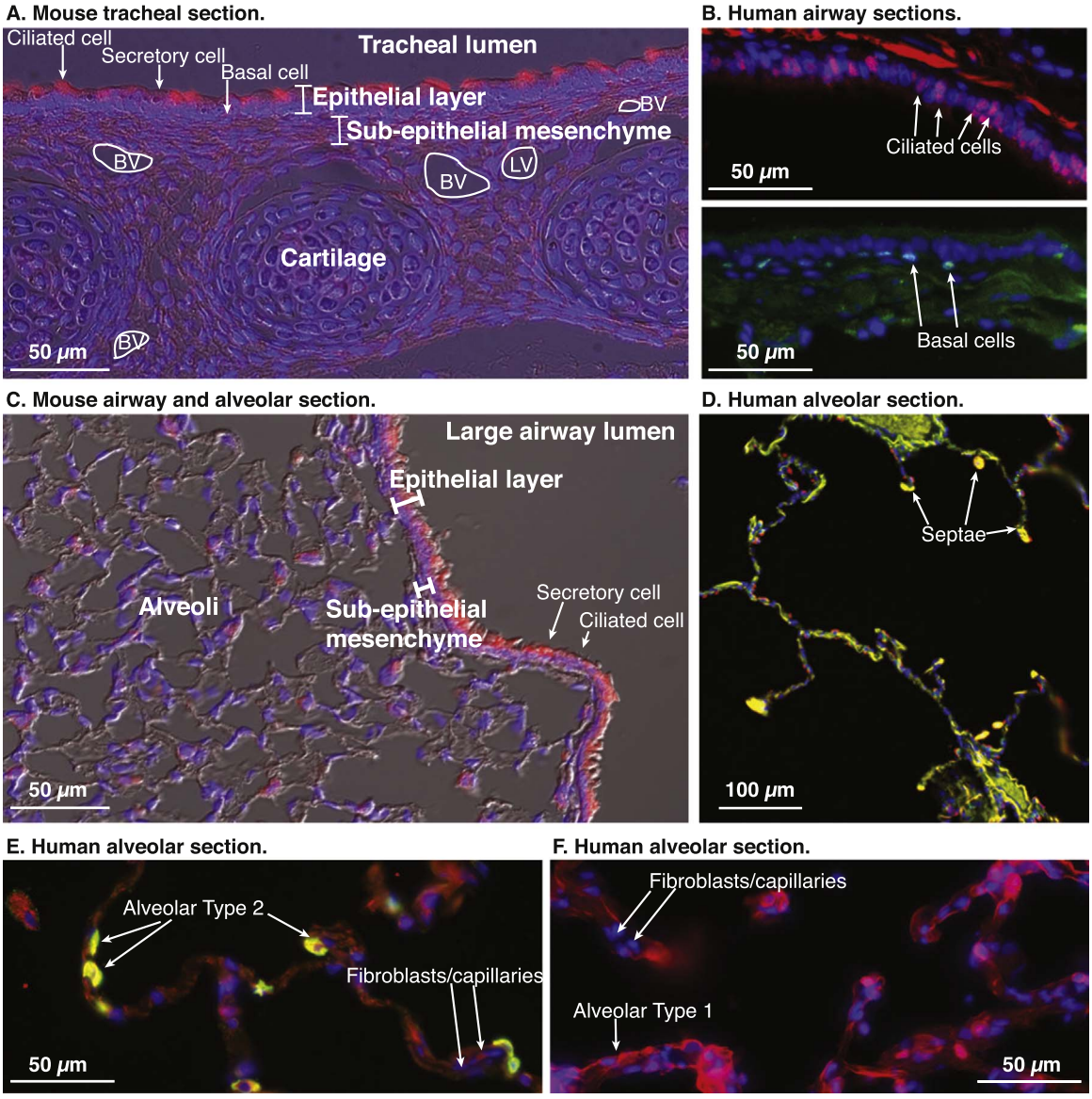

Fig. 1. Mammalian lung structure. A. Section of mouse tracheal epithelium with stained cilia (acetylated tubulin protein; red). The trachea is lined by an epithelial layer containing ciliated, secretory and basal cells. Underlying the epithelium is a layer of sub-epithelial mesenchyme, predominantly consisting of ill-characterized fibroblasts. The trachea is supported by cartilage rings (seen in cross-section) and smooth muscle (not visible; only present on the dorsal side) which are embedded within a more loosely-packed layer of fibroblasts. Blood vessels (BV) and lymphatic vessels (LV) are out-lined in white. B. Human airway sections stained to show ciliated cells (nuclear FOXJ1 protein: red), or basal cells (nuclear TP63 protein; green). C. Section of mouse lung showing a large airway and alveolar region with club cells and alveolar type 2 cells labelled (Fgfr2 protein; red). The airway is lined by an epithelium containing secretory and ciliated cells. Underlying the airway epithelium is a thin layer of mesenchyme, predominantly consisting of smooth muscle cells. The alveoli contain alveolar type 2 cells and type 1 cells, capillaries and multiple types of fibroblast. D-F. Adult human alveolar sections. D. Auto-fluorescence (green and yellow) outlines the alveolar structure with elastin fibres being particularly prominent. E. Alveolar type 2 cells (LPCAT1 protein; green) are dotted throughout the alveolar surface which is supported by various fibroblasts and capillaries. F. The membrane of alveolar type 1 cells (HOPX protein; red) lines the entire alveolar surface. Nuclei of fibroblasts and capillary populations can be seen within the septae.

neuroendocrine and brush cells. Airway epithelial composition depends on proximal-distal and dorso-ventral position; it is also likely that there is more epithelial heterogeneity than currently appreciated. Distally, the airways open out into the alveoli at the bronchoalveolar duct junctions in the mouse; or via respiratory bronchioles, which can comprise multiple alveolar ducts, in the human. In these regions the epithelium transitions to a more squamous morphology and the alveoli are lined by surfactant-secreting alveolar type 2 (AT2) cells and attenuated alveolar type 1 (AT1) cells which provide a minimal barrier for gas exchange.

The adult lung mesenchyme is much less-well characterized than the epithelium. Cartilage, and airway and vascular smooth muscle, are easily distinguished by morphology and position, but the various fibroblast populations are not. Fibroblasts are found throughout the airways and alveoli and can be loosely categorized based on position (tracheal, bronchiolar, alveolar, vessel-associated). Fibroblasts have been most carefully characterized in the alveolar region where, in mice, they are typically divided broadly into alveolar myofibroblasts (matrix-secreting, alpha smooth muscle actin; αSMA^{+}) and lipofibroblasts (roles in lipid trafficking and retinoid storage). However, the composition of lung fibroblasts also changes during development and there are clearly additional sub-types that require further characterization (Branchfield et al., 2016a; Endale et al., 2017; Moiseenko et al., 2017; Ntokou et al., 2015; Rock et al., 2011a).

The lung contains two separate branches of the blood circulatory system, plus a lymphatic network. The bronchial branch of the systemic circulation supplies lung cells with oxygen and nutrients and removes waste. Whereas, the pulmonary circulation carries deoxygenated blood to the alveoli for gas exchange. Vascular and lymphatic vessels are supported by a varying number of pericytes, smooth muscle cells and