The International Journal of Biochemistry & Cell Biology 56 (2014) 82–91

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review

Harnessing the potential of lung stem cells for regenerative medicine☆

Jonathan L. McQualter[a,*], Desiree Anthony[a], Steven Bozinovski[a], Cecilia M. Prêle[b,c], Geoffrey J. Laurent[b,c]

[a] Lung Health Research Centre, Department of Pharmacology and Therapeutics, University of Melbourne, Melbourne, Vic, Australia
[b] Centre for Cell Therapy and Regenerative Medicine, School of Medicine and Pharmacology, The University of Western Australia and Harry Perkins Institute of Medical Research, Perth, WA, Australia
[c] Lung Institute of Western Australia and Centre for Asthma Allergy and Respiratory Research, School of Medicine and Pharmacology, The University of Western Australia, Perth, WA, Australia

ARTICLE INFO

Article history:
Received 4 July 2014
Received in revised form 3 October 2014
Accepted 7 October 2014
Available online 15 October 2014

Keywords:
Lung
Stem cells
Regeneration
Epithelium
Mesenchyme

ABSTRACT

In response to recurrent exposure to environmental insults such as allergens, pollution, irritants, smoke and viral/bacterial infection, the epithelium of the lung is continually damaged. Homeostasis of the lung requires a balance between immune regulation and promotion of tissue regeneration, which requires the co-ordinated proliferation and differentiation of stem and progenitor cells. In this review we reflect on the current understanding of lung epithelial stem and progenitor cells and advocate a model hierarchy in which self-renewing multipotent lung epithelial stem cells give rise to lineage restricted progenitor cells that repopulate airway and alveolar epithelial cell lineages during homeostasis and repair. We also discuss the role of mesenchymal progenitor cells in maintaining the structural integrity of the lung and propose a model in which mesenchymal cells act as the quintessential architects of lung regeneration by providing molecular signals, such as FGF-10, to regulate the fate and specificity of epithelial stem and progenitor cells. Moreover, we discuss the current status and future prospects for translating lung stem cell therapies to the clinic to replace, repair, or regenerate diseased lung tissue. This article is part of a directed issue entitled: Regenerative Medicine: the challenge of translation.

Contents

Abbreviations: ALI, air–liquid interface; AT1, alveolar type I; AT2, alveolar type II; BADJ, bronchioalveolar duct junctions; BASC, bronchioalveolar stem cell; BM, bone marrow; BMP, bone morphogenetic protein; CCSP, club cell secretory protein; CFTR, cystic fibrosis transmembrane conductance regulator; CGRP, calcitonin gene-related peptide; COPD, chronic obstructive pulmonary disease; EGF, epidermal growth factor; ES, embryonic stem cells; FGF, fibroblast growth factor; GFP, green fluorescent protein; IPF, idiopathic pulmonary fibrosis; iPS, induced pluripotent stem cells; KGF, keratinocyte growth factor; MSC, mesenchymal stromal cell; NEB, neuroepithelial body; NGFR, nerve growth factor receptor; SP-C, surfactant protein C, TFtissue factor.

☆ This article is part of a directed issue entitled: Regenerative Medicine: the challenge of translation.

* Corresponding author. Tel.: +61 3 83448636.
E-mail address: jlmcq@unimelb.edu.au (J.L. McQualter).

http://dx.doi.org/10.1016/j.biocel.2014.10.012
1357-2725/

1. Introduction

Throughout life, exposure to environmental insults such as allergens, pollution, irritants, smoke and viral/bacterial infection continually damages and kills the cells of the lung. In response, the lung initiates a wound-healing response that promotes tissue regeneration through the co-ordinated proliferation and differentiation of stem and progenitor cells. However, failure to appropriately initiate or resolve the regenerative process in lung diseases is likely to play a critical role in the development and exacerbation of pathologic tissue remodelling, fibrosis and cancer. Hence, knowledge of the cell and molecular biology of lung regeneration and remodelling has enormous potential for tapping into the regenerative power of stem cells to maintain homeostasis of the lung. Most of the basic research demonstrating the regenerative potential of the adult lung has been undertaken using the mouse as a model organism. However, a recent case study has reported the observation of compensatory lung growth in a 33-year-old woman 15 years after a right-sided pneumonectomy for the treatment of lung cancer, which strongly supports the concept that the adult human lung has similar capacity for regeneration (Butler et al., 2012). In this review we discuss recent advances in the understanding of the organisation of endogenous stem and progenitor cells in the lung and their contribution to regeneration and repair of the adult lung.

2. The cellular composition of the adult lung

The mammalian lung is a highly complex organ comprising an ensemble of many different cell types organized in specialized anatomical structures, which serve a number of essential life functions. During development the lung originates from foregut endodermal progenitor cells that give rise to the trachea and two ventral lung buds that undergo branching morphogenesis to generate the conducting airways and millions of highly vascularized alveolar sacs, where respiration occurs (Warburton et al., 2005). The airway epithelium has key functions in microbial defense, immune regulation, mucociliary clearance of pathogens and toxins and acts as a physical barrier to exogenous particulate matter (Knight and Holgate, 2003). The submucosal glands are also major sites of mucous production and serous cells secrete electrolytes, antioxidants and antimicrobial and anti-inflammatory peptides.

In the adult mouse lung, the proximal airways comprise a pseudostratified epithelium lined with basal cells, interspersed by cartilaginous rings and submucosal glands. This transitions to a simple columnar epithelium without basal cells in the intralobar airways and terminal bronchioles. The cells lining the airways include club (formerly named Clara cells), ciliated, goblet, and neuroendocrine cells and submucosal gland mucous, duct and serous cells. The terminal bronchioles extend into the alveolar sacs, which contain highly specialized alveolar type II (AT2) and alveolar type I (AT1) cells (Fig. 1). In humans, the same cells are present but differ in their pattern of distribution along the respiratory tree. Submucosal glands, restricted to the trachea in mice, are found throughout the trachea and the first few generations of bronchi in humans. More goblet cells are also found in human proximal airways and the basal cell-lined pseudostratified epithelium extends distally all the way down to the small bronchiolar airways in the human lung. However, a number of studies have recently reported the expression of basal cell markers in the distal lungs of mice after virus infection (Byers et al., 2013; Kumar et al., 2011), which indicates that the cellular composition of the lung epithelium is influenced by environmental exposure. Therefore, one could speculate that the variance in cellular diversity between mouse and human lungs could be attributed, at least in part, to the specific pathogen-free conditions of laboratory housing.

In parallel with the development of the lung epithelium, mesodermal progenitors in the surrounding mesenchyme give rise to a diversity of cells including endothelium, chondrocytes, myofibroblasts, lipofibroblasts, smooth muscle, pericytes and other mesenchymal lineages (Fisher and Summer, 2006; Peng et al., 2013). These cells provide important signals that drive development of the lung epithelium and are key to the organization of the complex three-dimensional architecture of the lung. Moreover, they give rise to the highly specialized pulmonary vasculature, which facilitates gas-exchange through its intimate relationship with the alveolar epithelium. In light of this complexity, it is not surprising that researchers have identified numerous stem and progenitor cell populations that contribute to regeneration and repair of the adult lung.

3. Mouse lung epithelial stem and progenitor cells

Until recently, much of the evidence for the presence of stem and progenitor cells in the lung was implied from studies showing that the lung epithelium was able to regenerate after injury. Using experimental injury models, a number of studies have revealed that the adult lung epithelium is maintained by different populations of lung stem and progenitor cells residing in different anatomical regions throughout the respiratory tree. In some of the earliest studies, Evans et al. (1976) used tritiated thymidine to track epithelial cell fate after nitrogen-dioxide or ozone-induced bronchiolar injury to show that non-ciliated (club) cells were able to proliferate and give rise to ciliated and non-ciliated daughter cells. To test this concept further, researchers have exploited the cytochrome P450-mediated cytotoxic metabolism of naphthalene to selectively ablate club cells in bronchiolar airways of mice (Chichester et al., 1991). Using this model, numerous studies have indicated that a subset of naphthalene-resistant club cell secretory protein $(CCSP)^+$ cells, termed variant club cells, are largely responsible for regeneration of the bronchiolar airways (Giangreco et al., 2002; Guha et al., 2012; Hong et al., 2001). Variant club cells co-localize with neuroepithelial bodies (NEBs) in the bronchiolar airways and bronchioalveolar duct junctions (BADJs) of the terminal bronchioles. In contrast, epithelial regeneration was not observed after all CCSP-expressing cells were ablated using CCSP-tk transgenic mice, which express the herpes simplex thymidine kinase gene under the CCSP promoter (Reynolds et al., 2000). This suggests that $CCSP^+$ cells are indispensable for regeneration of the bronchiolar airways. In another influential study, Kim et al. (2005) described a population of BADJ-associated bronchioalveolar stem cells (BASCs), which express dual bronchiolar and alveolar lineage markers CCSP and surfactant protein (SP)-C, that are able to self-renew after lung injury and expand after the induction of oncogenic kras expression. These studies suggest that BASCs might be multipotent epithelial progenitors with the capacity to give rise to bronchiolar and alveolar epithelial cells; a concept that has provoked substantial debate over the last decade.

To directly test the contribution of putative stem and progenitor cells to epithelial regeneration, a number of inducible Cre recombinase transgenic mice crossed with floxed reporter strains have been used for lineage tracing studies. Using Scgb1a1-CreER/Rosa-LacZ mice, Rawlins et al. (2009) confirmed that $CCSP^+$ cells can self-renew extensively and give rise to ciliated cells in the bronchiolar airways during postnatal growth and after naphthalene injury. Other studies, using Scgb1a1-rtTA/Otet-Cre/Rosa-LacZ mice, have shown that $CCSP^+$ cells are the cellular origin of goblet cells induced by ovalbumin sensitisation (Chen et al., 2009). In contrast, lineage tracing studies in FoxJ1-CreER/Rosa-EYFP mice, in which ciliated cells are specifically labeled, have shown that ciliated cells are long-lived, terminally differentiated (Rawlins and Hogan, 2008)