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Review article

Organogenesis of adult lung in a dish: Differentiation, disease and therapy

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ABSTRACT

The remarkable regenerative capacity of the lung suggests that stem cells could be of therapeutic importance in diverse lung diseases; however, the successful exploitation of lung stem cell biology has long been hampered by our inability to maintain and expand adult lung stem cells while retaining their multi-lineage potential *in vitro*. Recently, advances in our understanding of stem cell niches and the role of key signalling modulators in controlling stem cell maintenance and differentiation have fuelled the development of new *in vitro* three-dimensional (3D) culture technologies that sustain the stem cell-driven formation of near-physiological, self-organizing structures called organoids. Here we review basic approaches to organoid model systems and highlight recent achievements in the generation of organoids from adult stem and progenitor cells of both the murine and human lungs. We evaluate current applications in studying cellular changes in proliferation, differentiation, plasticity, and cell polarity, and cellular and molecular crosstalk of epithelial cells with stroma. Advantages and limitations of organoids for clinical use are also discussed.

1. Introduction

The lung is a complex organ composed of numerous types of interconnected epithelial cells, stromal cells, including vascular cells and immune cells, and extracellular matrix (ECM) that synergize to maintain lung integrity. In the last decade there has been significant progress in understanding the organization of stem and progenitor cells in the adult lung. The analysis of lung injury models, combined with *in vivo* lineage-tracing techniques, has identified various potential epithelial stem and progenitor cells that respond to local injury and replace the damaged epithelial cells. These achievements have opened up a new era for the potential exploitation of adult stem cells in clinical applications for degenerative lung diseases arising from the impairment or depletion of specific cell types. However, historically it has been challenging to maintain and expand these stem cells and to direct their lineage specification to reproduce such physiological functions as airway patency, mucociliary clearance, and gas exchange *in vitro*. This is partly due to the limited reproduction of multi-cellular organization of the lung *in vitro*.

For decades, researchers have attempted to find suitable *in vitro* model systems that can recapitulate *in vivo* functions and processes, from molecular and cellular levels to whole tissue, and organ functions. Two-dimensional (2D) model systems, such as monolayer cell cultures, have been used to assess the clonogenicity of adult progenitor cells and to induce lineage differentiation of pluripotent stem cells. However, the lack of structural and physical supports provided by stromal components including the ECM, has been a barrier to understand cellular and molecular functions under physiological and pathological conditions. Recent progresses in isolating numerous types of cells, including epithelial progenitor cells and stromal cells, and defining niche factors that are important for lung development has led to the establishment of an *in vitro* three-dimensional (3D) lung culture system, termed lung organoid cultures. In organoids, epithelial stem and progenitor cells, cultured in ECM supplemented with either a mixture of growth factors or stromal cells, self-organize into complex structures retaining clusters of multi-lineage epithelial cells. Lung organoids recapitulate various features of the lung including heterogeneous cell composition, spatial organization and retention of a stem cell population harboring the capacity for both self-renewal and differentiation (Fatehullah et al., 2016). Importantly, lung organoids provide an *in vitro* model system for studying regenerative mechanisms of epithelial stem and progenitor cells proposed from *in vivo* studies.

In this review, we will focus on recent advances in the murine and human organoids derived from adult primary lung epithelial cells. This review will provide an overview of the potential of adult lung stem and progenitor cell that are responsible for lung homeostasis, regeneration, and enable the generation of organoids retaining multi-lineage epithelial cell types. The value of lung organoids as potent model systems for understanding tissue regeneration, lineage specification, and disease modelling will be evaluated. Future challenges for clinical application

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Table 1
Adult lung stem and progenitor cells capable of generating organoids in mouse and human.

location	Cell type	Markers for Isolation	Differentiation ability in 3D organoids
Tracheobronchiolar region	Basal cells	Krt5^{+}, Ngfr^{+}Itgα6^{+}, GSIβ4^{+} (mouse) Ngfr^{+}Itgα6^{+} (human) Ngfr^{+}CD166^{+}CD44^{+} (human)	Basal cells (Trp63+, Krt5+, Krt14+, Ngfr+, Pdpn+) Club cells (Scgb3a2, Splunc) Goblet cells (Muc5AC, Muc5B) Ciliated cells (Foxj1, Acetylated tubulin) (Rock et al., 2009, 2011a, 2011b; Hegab et al., 2012; Tata et al., 2013; Tadokoro et al., 2014; Danahay et al., 2015; Butler et al., 2016)
Bronchiolar region	Club cells	Scgb1a1^{+} (mouse)	Club cells (Scgb1a1) Goblet cells (Muc5AC) Ciliated cells (Foxj1, Acetylated tubulin) AT2 cells (Sftpc)
	Bronchioalveolar stem cells (BASCs)	EpCAM^{hi}Itgα6^{+}β4^{+}CD24^{low} (mouse) CD45^{-}CD31^{-}CD34^{-} (Lin^{-}) Sca-1^{low} (mouse) EpCAM^{+}CD24^{low}Sftpc-GFP$^{neg/low}$ (mouse) EpCAM^{+}Sca1^{+} (mouse)	(McQualter et al., 2010; Teisanu et al., 2011; Chen et al., 2012; Lee et al., 2014)
Alveolar region	AT2 cells	Sftpc^{+} (mouse) EpCAM^{+}Sca1^{-}CD24^{-}Sftpc-GFP^{hi} (mouse) EpCAM^{+}Sca1^{-} (mouse) EpCAM^{+}HTII-280^{+} (human)	AT2 cells (Sftpc) AT1 cells (Pdpn, Hopx, Ager) (Chen et al., 2012; Barkauskas et al., 2013; Lee et al., 2014; Jain et al., 2015)

will also be discussed.

2. Adult lung stem and progenitor cells

The adult lung is a highly quiescent tissue with a slow turnover rate (< 1% per day) of airway and alveolar epithelia (Bowden, 1983; Goss, 1966; Kotton and Morrisey, 2014). However, following tissue damage, lungs demonstrate extraordinary regenerative capacity to repair tissue damage and restore function. Recent advances in cell lineage tracing, flow cytometric analyses, and cell culture techniques have identified the specific stem and progenitor cells responsible for these extraordinary feats. In this review, we will focus on stem and progenitor cells capable of generating lung organoids. A brief overview is provided in Table 1.

2.1. *Epithelial stem and progenitor cells of the adult mouse lung*

Within the mammalian lung, there are a large number of epithelial cells along the pulmonary axis, stretching from the proximal to the distal end. This axis can be sub-divided into three regions, the tracheobronchial, bronchiolar, and alveolar region. Each region is lined by specialized epithelial cell types that are maintained by regional epithelial stem and progenitor cells with potential to generate lung organoids.

2.1.1. *Basal Cells*

Basal cells expressing Trp63, Krt5, and Ngfr lie close to the basal lamina and comprise ~30% of the pseudostratified mucociliary epithelium lining the trachea region. Lineage tracing studies have shown the maintenance of this region by basal and basal luminal precursor cells with a slow turnover during steady state (Ghosh et al., 2011; Mori et al., 2015; Mou et al., 2016; Rock et al., 2009; Watson et al., 2015). Following injury, basal cells demonstrate extensive proliferative and self-renewal capacity to differentiate into the mucous- and serous-secreting cells as well as ciliated cells, secretory goblet, and club lineage cells (Borthwick et al., 2001; Ghosh et al., 2011; Hegab et al., 2011; Hong et al., 2004a, 2004b; Rock et al., 2009). The Notch signalling pathway has been highlighted as playing a critical role in regulating the fate decision of basal cells between secretory lineage cells and ciliated cells (Carraro and Stripp, 2015; Pardo-Saganta et al., 2015; Rock et al., 2011b). Recently, club cells have been shown to revert into the lost basal cells post genetic ablation of basal cells *in vivo* suggesting the contribution of cellular plasticity to regenerative process (Pardo-Saganta et al., 2015; Tata et al., 2013). However, the molecular mechanisms how these differentiated cells work together with stem or progenitor cells to maintain lung integrity still remain to be fully elucidated.

2.1.2. *Club cells*

Club cells expressing secretoglobin family 1a member 1 (Scgb1a1, also known as CC10 or CCSP) are columnar epithelial cells comprising the majority of the bronchiolar epithelial region. Given their capacity for both self-renewal and differentiation into ciliated cells over the long-term, club cells have been considered stem cells in the bronchiolar epithelium at steady state (Rawlins et al., 2009). Following the administration of naphthalene to selectively ablate club cells, naphthalene-resistant variant club cells near to neuroendocrine bodies (NEBs) and bronchioalveolar duct junctions (BADJs) have been revealed to replenish the bronchiolar epithelium (Giangreco et al., 2002; Hong et al., 2001; Rawlins et al., 2009; Reynolds et al., 2000; Stripp et al., 1995). By exploiting the bleomycin- and influenza-induced alveolar injury models, club cells have been demonstrated to produce alveolar lineage cells (Rock et al.., 2011b; Tropea et al., 2012; Vaughan et al., 2015; Zuo et al., 2015). At BADJ regions, bronchioalveolar stem cells (BASCs) expressing both Scgb1a1 and Sftpc, which are the markers for club and alveolar type II cells (AT2) respectively, have been suggested to be stem cells that can expand after naphthalene- and bleomycin-induced injury *in vivo* (Kim et al., 2005). These cells also show multi-lineage differentiation into bronchiolar and alveolar lineages *in vitro* in the 3D organoid culture system (Lee et al., 2014). Endothelial derived Thrombospondin-1 has been suggested to induce alveolar lineage differentiation of BASCs during bleomycin-induced alveolar damage repair. In response to cytokines such as IL-13, club cells can also generate goblet cells (Atherton et al., 2003; Wills-Karp et al., 1998; Zhu et al., 1999). Despite of these advances in identifying the multi-potent differentiation capacity of club cells, the heterogeneic response of club cells to different injuries and the molecular mechanisms regulating bronchiolar- and alveolar-lineage differentiation remain to be uncovered.

2.1.3. *AT2 cells*

The distal alveolar region is lined by surfactant-producing AT2 and gas-exchanging AT1 cells. Lineage tracing studies have shown that AT2 cells function as stem and progenitor cells that self-renew and give rise to AT1 cells in the steady state and during regeneration after injury

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