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Lung Stem cell biology

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Abstract

Over the past few years new insights have been added to the study of stem cells in the adult lung. The exploration of the endogenous lung progenitors as well as the study of exogenously delivered stem cell populations holds promise for advancing our understanding of the biology of lung repair mechanisms. Moreover, it opens new possibilities for the use of stem cell therapy for the development of regenerative medicine approaches for the treatment of lung disease. Here, we discuss the main types of lung epithelial progenitor populations; the potential of endothelial progenitors, mesenchymal stem cells and embryonic stem cells for lung therapy; as well as summarize the cellular mechanisms involved. The de it provides novel insights for the development of regenerative medicine approaches for the treatment of lung disease.

1. Introduction

Lung disease is one of the leading causes of death in the world. Current treatments are focused on improving the quality of life of lung disease patients by reducing inflammation or pharmacologically inhibiting disease specific pathways [1]. Regenerative medicine treatments that attempt to reverse structural damage to the lungs are scant at best. Focused on harnessing the power of stem cells, regenerative medicine attempts to utilize the body's inherent regenerative capacities to restore function to damaged cells, tissues and organs.

Here, we provide a concise summary of the current knowledge and challenges regarding the main lung progenitor populations (Figure 1), the mechanisms regulating their behavior and their potential to initiate or augment lung repair.

2. Endogenous Lung Stem and Progenitor Cells

Rapidly renewing tissues contain rare populations of tissue specific adult stem cells that have the capacity to proliferate and give rise to transit amplifying cells which in turn can give rise to differentiated cells. In some tissues, fully differentiated cells can also be stimulated to proliferate upon homeostatic pressure or injury. These cells, usually termed facultative progenitor cells, a) show highly infrequent proliferation, but, following injury, they can undergo transition to a continuous proliferation state and b) possess the ability to transition from a differentiated state to an undifferentiated state and vice-versa between normal and injury/repair conditions [2].

Although cells with both stem cell and facultative progenitor cell characteristics have been identified in the lung, their classification has been challenging and, it is still questionable whether adult lung stem cells exist. Studies in mice have shown that, under normal conditions, these progenitor cells are sufficient to maintain the epithelium [3]. However, evidence for their capacity to regenerate the lung following acute injury is still lacking. Nevertheless, several studies have identified airway epithelial cells that have the ability to enter the cell cycle after injury to the lungs and thus be considered as facultative progenitor cells: basal, Clara-like, Clara, pulmonary neuroendocrine, and alveolar type 2 cells [4]. These cells show high regional specialization of functions [5]. The lung microenvironment, containing a number of different cell types, diverse extracellular matrix proteins and other growth factors, constitutes a “stem cell niche”, which is essential in determining the progenitor cells' function and differential potency [5]. As a result, resident lung progenitor cell populations can further be classified by their location in the lung: intralobar airways, tracheobronchial region, bronchiole-alveolar duct junctions, and the alveoli.

2.1 Intralobar Airways

The columnar epithelium lining the distal intralobar airways of the mouse lung is mainly composed of multiciliated and secretory cells, lacking basal cells. Early experiments have shown that mature ciliated cells are postmitotic and thus do not contribute to the maintenance of the airway epithelium under steady-state conditions or in response to injury [8]. In contrast, several studies have shown that, following injury to the mouse bronchioles, Clara like cells can both self-renew and give rise to new ciliated cells [6-8]. For instance, it has been shown that a special subset of Clara cells known as variant Clara cells, which are resistant to naphthaelene injury, have the potential to self-renew and generate ciliated cells, making them candidate stem cells of the intralobar airway epithelium [9,10]. However, it is uncertain whether these cells are actually naphthalene-resistant secretory cells or simply immature secretory cells that lack enzymes for naphthalene metabolism [3]. It is hypothesized that the niche for these variant Clara cells are the neuroepithelial bodies that contain clusters of neuroendocrine cells [11]. However, the precise peptides and growth factors secreted by neuroepithelial bodies that act on adjacent secretory cells are still largely unknown though [10]. In addition, naphthalene resistant Clara cells have been identified at the bronchioalveolar duct junction (BADJ) [2,10]. These cells co-express *Scgb1a1* (Secretoglobin 1a1), a marker of Clara cells, and an alveolar type 2 cell marker Surfactant protein C (SftpC) and proliferate upon lung injury. Based on their in vitro differentiation potential, it has been proposed that they are bronchioalveolar stem cells (BASCs) that give rise to both bronchiolar and alveolar cells in vivo [12] [13]. However, further studies using lineage tracing demonstrated that there was no contribution of lineage tagged Clara cells to alveolar epithelia during either steady state homeostasis or after hyperoxic injury [12]. Other identified stem cell populations in the intralobar mouse airways include EpCAMhi/CD104+/CD24- cells [14].

2.2 Tracheobronchial region

The tracheobronchial region is also known as the lung airways and extends from the trachea to the terminal bronchioles. Basal cells being positive for protein markers such as Trp63, cytokeratin 5 (ck5), cytokeratin 14 (ck14) and nerve growth factor receptor (Ngfr) constitute

3. Circulating and exogenously administered stem/progenitor cells

3.1 Endothelial progenitor cells

Endothelial progenitor cells (EPCs) were originally described as circulating bone marrow-derived cells that possess the potential to proliferate and differentiate into mature endothelial cells [27,28]. EPCs can therefore provide a circulating pool of reservoir cells that could potentially integrate into the site of lung injury and replace damaged endothelium. In addition, isolation and exogenous manipulation of EPCs can constitute a cell source for cell therapeutic approaches for lung injury.

However, no clear consensus regarding the identity of EPC cells exist and the term is used to describe a number of cell types with putative roles in vascular homeostasis and disease [29,30]. Nevertheless, there is some agreement that two main types of EPCs can be isolated from human peripheral blood and cultured in vitro: early EPCs and late outgrowth EPCs. Early EPCs are CD34+ CD31+ CD14+, have a spindle shape morphology, grow early in vitro, cannot form tubes in a matrigel tube forming assay, and secrete high levels of growth factor and cytokines. Late outgrowth EPCs appear after 2 weeks of culture, are CD31+ CD144+ CD146+ CD105+ CD45- CD14- CD115-, have cobblestone-like shape and possess the unique ability to spontaneously form human blood vessels in certain environments. In the context of the lungs, it is postulated that early EPCs can act as paracrine cells while late EPCs can function to restore vasculature structures [4]. Indeed, when infused together the two seem to play a synergistic role in restoring vascular structure and function [31]. Interestingly, resident microvascular endothelial progenitor cells have been identified in the pulmonary microvascular endothelium of mouse, rat and human lung [32]. These cells seem to possess rapid vasculogenic capacity compared to EPCs derived from other sources [32].

In vivo, circulating EPCs can be recruited from the periphery and potentially integrate in sites of injury and promote repair by enhancing neovascularization. This can happen by either their direct differentiation to more mature vascular cells or by the release of paracrine factors that promote cell growth and angiogenesis [33]. Disease state, age and lifestyle choices, all have been shown to reduce EPC counts and their potential reparative capacity (reviewed in [34] and references therein). Recent evidence suggests that hypoxia might play an important role in EPC mobilization, growth and differentiation, however, the precise mechanisms are unclear. Still, the numbers of circulating EPCs do seem to correlate with lung disease states. For example, increased circulating EPC numbers generally correlate with better survival and less residual lung [35-37]. However, there are cases such as non-small cell lung cancer where increased numbers of circulating EPCs correlates with worse survival [38,39].

3.2 Mesenchymal Stem cells

Perhaps the best researched of non-resident stem cells of the lung are bone marrow derived mesenchymal stem cells or mesenchymal stromal cells (MSCs). It is important to note that MSCs represent a “heterogeneous” population expressing different levels of a panel of cell surface markers which, although not specific, in combination are associated with defining MSCs. MSCs are further defined by cell attachment, self-renewal, clonogenicity, and the

ability to differentiate towards multiple lineages [40,41]. The minimal criteria for defining human MSCs as recommended from the according to the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy as of 2006, is as follows: a) plastic adherence in standard tissue culture conditions, b) expression of CD73, CD90, and CD105 c) no expression for CD 11bCD14, CD34, CD45, CD79 α /CD19, and HLA-DR-, and d) differentiation in vitro to osteoblasts, adipocytes, and chondroblasts [42]. Interestingly, MSC-like cells have been isolated from adult mouse [43-45] and human lungs [46-48]. However, the physiologic importance of these cell populations is still under investigation.

Transplantation of MSCs offers many advantages for regenerative therapy as MSCs are immunologically well tolerated, which allows for administration of allogenic MSCs without significant host responses[49]. Furthermore, they can be expanded ex vivo and easily manipulated genetically to enhance their survival and engraftment as well as the delivery desired molecules [50]. While a major effort in MSC research has been focused on their regenerative capacity, several studies have reported that MSCs can play a role in tissue repair by the secretion of paracrine factors that activate cytoprotection, cell growth, neovascularization and immunomodulation [40,51,52].

In regard to lung therapy, MSCs can be induced in vitro to express markers of either airway or alveolar epithelial cells [53]. However, since it is a rare event [54] emphasis has been shifted to their paracrine properties (Figure 2). For example, soluble mediators released by MSCs such as IL-1 receptor antagonist, IL-10, keratinocyte growth factor, hepatocyte growth factor, angiopoietin 1, and TGF β appear to play a significant role in the repair of acute and fibrotic injuries ([55-57]; also summarized in [4]), however the actual mechanisms by which they do this are not yet fully understood. Of note, several studies support a role of MSC in lung inflammation and injury by modulation of the immune system. Indeed, MSCs secrete anti-inflammatory agents such interleukin 1 receptor antagonist interleukin-6, interleukin-10, and prostaglandin E2 [58] while in parallel can suppress pro-inflammatory cytokine expression (i.e. TNF- α stimulated gene/protein 6) [54]. In addition, MSCs can also secrete anti-microbial peptides such as LL-37[59] and tumour-necrosis-factor-alpha-induced-protein-6 [60,61]. Indeed, in vivo delivery of mesenchymal stem cells increased bacterial clearance and enhanced host cell phagocytosis in septic mice [61,62].

3.3. Embryonic Stem Cells, Induced Pluripotent Stem Cells

Embryonic stem cells (ESCs) are derived from the ICM of the blastocyst. They are undifferentiated, pluripotent cells. In well-defined culture, they can be maintained indefinitely in this state, or they can be directed towards a specific cell fate [63]. Recently it was shown the stem cells could be generated from somatic cells by cellular reprogramming [64]. These induced pluripotent cells (iPS), although are not as robust or pluripotent as human embryonic stem cells, they do appear very similar morphologically and do possess the same ability to differentiate into cell types from all three germ layers [64].

This raises the possibility that epithelial cells could be created from somatic cells, which would allow for patient-specific iPS stem cells or the generation of gene-corrected iPS cells for individual with genetic diseases such as cystic fibrosis [65], alpha-1-antitrypsin deficiency [65].

Several studies over the past few years have shown that both mouse and human ESCs can be induced in culture to generate cells with phenotypic characteristics of type 2 alveolar epithelial cells. These include expression of surfactant proteins and lamellar bodies, formation of pseudoglandular structures [66]. Moreover, it has been shown that intratracheal administration of the AECII cells derived from hESCs in a bleomycin-induced lung injury mouse model resulted in the engraftment and hESCs -derived SPS expressing cells. Importantly, mice receiving the AECII cells derived from hESCs showed significant reduction in lung injury compared to controls [67]. Using a similar model of lung injury, Soh and colleagues have shown recently that transplantation of hESCs and iPS derived CD166+ lung epithelial progenitor cells resulted in enhanced survivability of mice and improved lung pulmonary functions [68]. Despite the progress, generation of lung epithelia from ES or iPS and their therapeutic application remain challenging. These challenges include the complexity and lack of knowledge of the lung epithelia cell phenotype, the need for improved protocols and the tumorigenicity of the implanted due to the presence of undifferentiated pluripotent stem cells.

4. Challenges and Future directions

Despite the progress, uncovering the mechanisms by which progenitor/stem cell populations in the lung maintain homeostasis has been prove to be very challenging. One of the most significant challenges is the identification of appropriate/specific marker for endogenous lung stem/progenitor cells population in both rodent and humans. Progress has been additionally slowed by the complex 3D structure of the lung, which has made it difficult to perform live monitoring of progenitor cells or of any microcellular interactions during development and repair. The development of better genetic tools (cell lineage tracing methods) as well advancements in the area of tissue engineering (to allow 3D studies *ex vivo*) can significantly contribute to the further development of the field. In addition, significant gaps remain in our knowledge regarding the development of lung cell therapy protocols. Indeed optimal methods for cell administration, dosage regimens and efficacy still need to be addressed. Future studies hold promise for providing new insights into the biology of lung stem cells as well for the translation of pre-clinical studies to new therapeutic modalities for lung disease therapy.

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Cell Type	Markers	Lineages
Basal Cells	Trp63+, Krt5+/Krt14+, NGFR+,	- Ciliated
	Pdpn+	- Secretory
Alveolar epithelial type II cells	Sftpc+	- Alveolar epithelial type I cells
Clara cells	Scgb1a1+	- Ciliated
		- secretory (including goblet)
Clara variant cells	Scgb1a1+, +/- Upka3/Scgb3a2	- ciliated
		- secretory
Distal lung progenitors	Itga6b4+, Sftpc-, Scgb1a1-, Krt5-	- Scgb1a1+
		- Sftpc+
Distal airway stem cells	Krt5+ Trp63+	- Alveolar pods of epithelial cells
Bronchioalveolar stem cells	Scgb1a1+, Sftpc+	- Sftpc+
		- Scgb1a1+
Submucosal gland duct cell	K14+, K18+	-

Figure 1. Summary of resident stem and progenitor cell types in the lung. Table modified from [69].

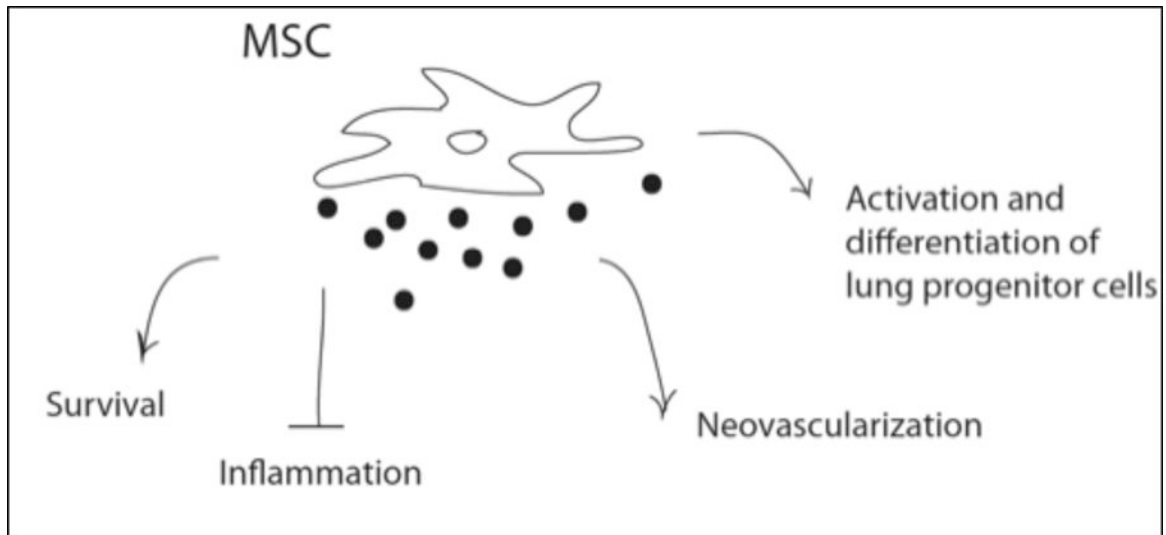


Figure 2.
Overview of MSC paracrine effects in the lung.

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