Stem Cells and Lung Diseases

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Abstract
This paper is designed to review our current understanding of the role of stem and progenitor cells in lung repair after injury and to review the current status of cell therapy approaches for lung diseases. It was found that circulating EPCs (endothelial progenitor cells) play roles in both acute lung injury and in fibrotic lung diseases. Circulating fibrocytes can contribute to the pathophysiology of fibrotic lung diseases and thus may be a potential therapeutic target. MSCs (mesenchymal cells) suppress lung injury and inflammation in several mouse models of inflammatory and immune-mediated lung diseases. In addition, novel areas of investigation have developed that include increasing exploration of three-dimensional culture systems and bioengineering approaches to generate functional lung tissue ex vivo and in vivo.

Glossary and Definition of Terminology

Potency: Sum of developmental options available to cell.

Totipotent: Ability to (re)generate an organism in total. In mammals only the zygote and the first cleavage blastomeres are totipotent.

Pluripotent: Ability to form all lineages of body. Example: embryonic stem cells.

Multipotent: Ability of adult stem cells to form multiple cell types of one lineage. Example: hematopoietic stem cells.

Unipotent: Cells form one cell type. Example: spermatogonial stem cells (can only generate sperm).

Plasticity: Hypothesis that somatic stem cells have broadened potency and can generate cells of other lineages, a concept that is controversial in mammals.

Embryonic stem cell: Cells isolated from the inner mass of early developing blastocysts. Embryonic stem cells have the capacity for self-renewal and are pluripotent, having the ability to differentiate into cells of all embryologic lineages and all adult cell types. However, embryonic stem cells cannot form extraembryonic tissue such as trophectoderm.

Adult stem cell: Cells isolated from adult tissues including bone marrow, adipose tissue, nervous tissue, skin, umbilical cord blood, and placenta that have the capacity for self-renewal. In general, adult stem cells are multipotent, having the capacity to differentiate into mature cell types of the parent tissue. Some populations of adult stem cells, such as mesenchymal stem cells exhibit a range of lineage differentiation that is not limited to a single tissue type. Whether adult stem cells exhibit plasticity and can differentiate into a wider variety of differentiated cells and tissues remains controversial.

Adult tissue-specific stem cell: The same as adult stem cells but with defined tissue specificity. A relatively undifferentiated cell within a given tissue that has the capacity for self-renewal through stable maintenance within a stem cell niche. Adult tissue-specific (endogenous) stem cells have a differentiation potential equivalent to the cellular diversity of the tissue in which they reside. The hematopoietic stem cell is a prototypical adult tissue stem cell.

Progenitor cell: A collective term used to describe any proliferative cell that has the capacity to differentiate into different cell lineages within a given tissue. Unlike stem cells, progenitor cells have limited or no self-renewal capacity. The term “progenitor cell” is commonly used to indicate a cell can expand rapidly, but that undergoes senescence after multiple cell doublings.

Introduction

Stem cells³,⁴ are defined as “Cells that have clonogenic and self renewing capabilities and that differentiates into multiple cell lineages”. These can be intrinsic or extrinsic in nature (Fig. 1).

Characteristic feature includes:⁵
1. Undifferentiated cells.
3. Infrequent proliferation.
4. Replenish progenitor cells.

For long-term maintenance of the stem cell, its proliferation must be accompanied by at least one of the progeny retaining the stem cell character of its parent. Scientist has long thought that these stem cells have the capacity for the production of more committed progenitors and could play an important role in repair and regeneration process in lungs. Experimental studies have been done to elucidate the various cell types involved in these reparative process.15

Embryonic Stem Cells

Reports16,17 show derivation of lung-specific cell phenotypes from embryonic stem cells (ESC) using small airway growth medium (SAGM). This group later identified a definitive medium for the differentiation of ES cells into alveolar epithelium and showed that murine ESCs cultured in this defined medium could be induced to express the type II pneumocyte marker surfactant protein-C (SPC). Evidence does suggest that, apart from their ability to proliferate and replicate themselves, embryonic cells that form tissues during embryonic development are different from the adult cells that maintain and repair them after birth.10

The majority of the genes expressed in multipotent embryonic progenitors are not expressed by endogenous lung stem cells or in adult lung. Embryonic cells proliferate rapidly and undergo shape changes that mediate branching morphogenesis and patterning in terms of tissue development which lead eventually to organ formation.11 Even though human embryonic stem cells have been shown to generate cell types found in the lung, differentiation has not been consistently directed efficiently towards a single cell lineage. There have been concerns, however, with the potential for malignant transformation and immune rejection in hosts.12 An elegant experiment highlighted this potential in a mouse model of gastric cancer. In this model C57BL mice were myeloablated and transplanted with gender-mismatched, GFP-labeled bone marrow. The mice were then infected with Helicobacter felis, which leads to chronic inflammation and gastric carcinoma. Furthermore, research with these cells involves the destruction of an embryo, and as such has met with moral and ethical objections.

Adult Stem Cells

Adult stem cells can be phenotypically characterized13,14 into Hematopoietic stem cells, Mesenchymal stem cells, Neural stem cells, Hepatic stem cells, Pancreatic stem cells, Skeletal muscle stem cells, Skin stem cells, Epithelial stem cells of lung, etc. A potential advantage of using stem cells from an adult is that the patient’s own cells could be expanded in culture and then reintroduced into the patient. The use of autologous cells would help avoid some of the problems associated with immunologic rejection. In a study published in 2001, a single Hematopoietic stem cell derived from adult bone marrow was transplanted from an adult male mouse into a female that had been lethally irradiated to ablate the resident bone marrow. This single donor cell was able not only to repopulate all bone marrow cell lineages but also engrafed several organs (Plasticity). Up to 20% of the lung parenchyma in the donor mouse was found to contain a Y chromosome, which colocalized with epithelial markers.15

Reports suggests that engrafment of bone marrow-derived stem cells as airway and alveolar epithelium is likely to occur but a very low rate (0.01 to 0.1%) of doubtful clinical significance.16

Moreover, chimerism or lung engrafment with adult marrow-derived cells has not been found in all studies. Further, data from several of the mouse studies have been questioned in light of more rigorous techniques and significant controversy exists as to the degree of chimerism or engrafment of adult marrow-derived cells that might actually occur.17,21 Further suggestion that adult marrow-derived cells acquire the phenotype of lung cells is provided by examination of morphologic appearance and/or coexpression of markers including cytokeratin (epithelium), smooth muscle actin (myofibroblast), or prosurfactant protein B or C (type 2 alveolar epithelium)22. These markers are not significantly expressed in populations of adult marrow-derived cells, suggesting that cells recruited to the lung have undergone phenotypic conversion. A number of studies suggest a functional implication for recruitment of adult marrow-derived cells to the lung. In an important proof-of-concept demonstration, ex vivo transduction of MSCs isolated from patients with cystic fibrosis (CF) resulting in expression of normal CF transmembrane conductance regulator (CFTR) was able to partially correct defective CFTR-dependent chloride current when ex vivo–transduced cells were mixed in culture with primary airway epithelial cells obtained from patients with CF.23 Preexisting injury increases recruitment of adult marrow-derived cells to the lung. This suggests that chemotactic signals released by injured or remodeling lung serve to attract marrow-derived cells. Similarly, expression of specific adhesion molecules or other proteins by injured or remodelling lung may be important for recruitment of adult marrow-derived cells.24

A number of soluble factors released by airway epithelium mediate recruitment of mature circulating leukocytes from bone marrow to the lung. Prominent among these is stromal-derived factor (SDF-1, CXCL12), which interacts with the CXCR4 receptor on the HSC surface.25 Adult MSCs can be induced to develop phenotypic characteristics of fibroblasts, osteoblasts, chondrocytes, or adipocytes by in vitro exposure to growth factors and cytokines.26 In contrast to engrafment and repair of the respiratory epithelium, there is accumulating evidence for the contribution of bone marrow-derived stem cells to the fibroblast/myofibroblast community in the lungs via circulating fibrocytes. Fibrocytes are circulating cells expressing the HSC marker CD34 and collagen. In fact, 80% of type 1 collagen-expressing fibroblasts were shown to be of bone marrow (donor) origin at sites of lung fibrosis in a mouse bleomycin model.27 There is also convincing evidence for engrafment into pulmonary vasculature by other bone marrow progenitors; endothelial progenitor cells. EPCs have been isolated from the bone marrow of rats and shown to express endothelial markers and engraf into areas of vascular injury in animal models of pulmonary hypertension.28

Endogenous Stem Cells

Endogenous tissue stem cells are undifferentiated cells that have been identified in nearly all tissues and are believed to contribute to tissue maintenance and repair. These are rare, unspecialized cells that are often localized to specialized niches within each tissue and usually cycle infrequently. These cells exhibit self-renewal capacity—they can produce more unspecialized cells—and can also give rise to daughter cells known as progenitor cells or transit-amplifying cells. At least three distinct regions have been described that support populations of lung tissue stem cells: intercartellagenous regions of tracheobronchial airways, neuroepithelial bodies (NEB) in bronchioles, and the bronchoalveolar duct junction (BADJ).29

Progenitor cells have a finite life span more robust proliferative potential, such as toxin-resistant cells, Clara cells, basal cells, etc.).
Endogenous progenitor cells may also be attractive candidates for targeting with gene transfer vectors that provide sustained expression.

**Therapeutic Potential of Stem Cells**

1. ARDS (regeneration of extracellular matrix)
2. Emphysema (regeneration of alveoli and extracellular matrix)
3. Lung fibrosis (regeneration of extracellular matrix)
4. Cystic Fibrosis (stem cells acting as genetic vectors)
5. Pulmonary arterial hypertension (Endothelial progenitor cells transduced with nitric oxide synthetase)
6. Lung cancer (targeting endogenous stem cells with potential for malignant transformation by identifying with specific surface markers)

**Tissue Engineered Lung**

Lung is composed of a complicated three-dimensional structure requiring precise alignment of airspace and vasculature to exchange gas. The extracellular matrix plays a major role in both this structural organization, and not surprisingly, in many of the diseases that afflict humans. Biomaterials designed for use as matrix for regenerative medicine purposes fail to replicate the complexity of the ECM that is found in the lung. The nature of complex organs such as the lung may even require the development of hybrid scaffolds formed from more than one material to provide all of the above requirements. For development of lung tissue the scaffolding or matrix must also remain long enough to support cell growth and tissue development without impeding the elasticity or altering the elastic recoil of the engineered tissue or the surrounding normal lung tissue. In the lung ECM contributes to the overall mechanical properties of the lung which change after injury or disease. If a biomaterial designed for use in the lung is not as elastic as normal lung it could potentially contribute to development of a restrictive condition similar to what is caused by the restrictive scar tissue formation seen in idiopathic pulmonary fibrosis or sarcoidosis patients. Both synthetic and natural polymers have been studied for use in lung tissue engineering. Natural materials that have been used to grow lung tissue include collagen, Matrigel and Gelfoam. In vivo use of these natural scaffolds has been shown to support tissue growth although development of lung tissue using these materials has not been substantial. One of the best sites in the body to test implantation of relatively unvascularized engineered tissues will be the lung. For in vivo implantation techniques to be successful the metabolic and therefore oxygen needs of the implant need to be met. The pleural cavity is an oxygen rich environment and even without support of blood flow in the lung direct diffusion to be met. The pleural cavity is an oxygen rich environment and even without support of blood flow in the lung direct diffusion

**References**


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