Published in final edited form as:
Expert Rev Respir Med. 2007 August ; 1(1): 157–165. doi:10.1586/17476348.1.1.157.

Circulating progenitor cells in chronic lung disease

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Abstract

Tissue regeneration and repair are fundamental both to recovery of the lung from injury and to the pathology of many chronic lung diseases. There are two potential sources for the adult progenitor cells that participate in this reparative process: resident lung progenitors and bone marrow-derived circulating cells. Bone marrow-derived cells, in particular, have been shown to give rise to airway and alveolar epithelial cells as well as lung mesenchymal cells. Emerging data has linked specific chemokine ligand-receptor interactions to the recruitment of these cells to the lung, and has implicated these cells in chronic lung disorders such as asthma and interstitial lung diseases. In this review, we summarize the current understanding of the biology of adult circulating progenitors as related to lung disease.

Keywords

stem cells; fibrocytes; chemokines; regeneration

Introduction

Tissue regeneration and repair is fundamental to the recovery of lung from injury, and dysregulation of this process is a hallmark of many chronic lung diseases. Aberrant regeneration is a central feature of many lung diseases; examples include airway remodeling in asthma, chronic bronchitis, and bronchiectasis; localized lung scarring in chronic lung infections such as mycobacterial and fungal infections; environmental interstitial lung diseases such as pneumoconiosis and hypersensitivity pneumonitis; and interstitial lung diseases of unknown cause, such as sarcoidosis and the idiopathic interstitial pneumonias. The source of the cells that are involved in these regenerative and fibrotic processes is therefore of substantial interest.

Unlike embryonic stem cells, which are capable of giving rise to daughter cells from all three germ layers, adult progenitor cells can differentiate into a more limited number of mature cell types (1); no single adult progenitor cell has been found to give rise to all lung cells, for example. Some investigators reserve the phrase “stem cell” for totipotent embryonic progenitor cells, to avoid the suggestion that adult progenitors have a similar capacity for differentiation (2–4). Adult bone marrow mesenchymal stem cells, first described as bone marrow-derived fibroblast precursors (5, 6), are adherent cells in culture and can be passaged at near the Hayflick limit (7, 8). Mesenchymal stem cells constitute a

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heterogenous population, and while, under defined culture conditions and in the presence of appropriate growth factors, they can be differentiated into osteoblasts, chondroblasts, adipocytes, or stromal cells, individual mesenchymal stem cells have a limited capacity of differentiating into only one or two cell types (7, 8). In transfer experiments, human mesenchymal stem cells given to SCID mice (9) and eGFP-transduced autologous baboon mesenchymal stem cells (10) were found to have engrafted in diverse tissues, including the lung. In distinction from mesenchymal stem cells, multipotent adult progenitor cells, are another bone marrow derived population that can be cultured indefinitely with very few growth factors and are capable of differentiating into cells from each of the three germ layers (11). It has been suggested that multipotent adult progenitor cells may represent a progenitor of mesenchymal stem cells, and also that their plasticity may be an artifact of in vitro culture conditions (8, 11).

Stem- and progenitor- cells are typically identified flow cytometrically as a “side population”, based on their expression of ABC superfamily multidrug efflux pumps and consequent rapid efflux of, and lack of staining with, the DNA-staining fluorochrome, Hoechst 33342 (12, 13). Using this technique, adult progenitor cells are found in many organs, including the lungs (1, 14–20). Lung side population cells are heterogeneous with respect to derivation from bone marrow and resident cells, with respect to expression of the common leukocyte marker CD45, and with respect to their ability to differentiate into epithelial, endothelial, and mesenchymal cells (21). In this context, circulating adult progenitor cells have recently been found to be recruited to the lung during regenerative and fibrotic processes and to interact with resident mesenchymal cells in the repair process (22–32). These circulating progenitor cells reside primarily in the bone marrow and traffic to new tissue micro-niches via the circulation, where they undergo differentiation into specific cellular lineages, integrate into the new microenvironment, and function in a tissue-specific manner (22–24, 30).

Irrespective of their source, the mechanism by which stem- or progenitor- cells give rise to new tissue has been the subject of controversy in the literature: the debate centers on the relative contribution of plasticity (ability of a progenitor cell to differentiate into various differentiated cells), transdifferentiation (ability of a differentiated cell of one tissue to differentiate into another differentiated cell) and fusion between a progenitor cell and a differentiated cell (33, 34). These mechanisms are not necessarily mutually exclusive and, to date, there is in vivo evidence for plasticity in the context of the lung (11, 33, 34) and at least in vitro evidence for fusion of mesenchymal stem cells with bronchial epithelial cells (35).

The current review focuses on these cirulating lung progenitor cells. These include epithelial progenitors that have been shown to be recruited to the lungs (4, 27–29, 32, 36, 37), bone marrow-derived endothelial progenitor cells, and mesenchymal progenitors, originally discovered for their contribution to wound repair and dubbed fibrocytes (23), which are now known to be involved in several lung diseases (25, 26, 30, 38).

Circulating progenitors of lung epithelial cells

A. Airway epithelium

Several lines of evidence document repopulation of lung epithelial cells from an extra-pulmonary source: transplantation of GFP-expressing bone marrow into lethally irradiated mice has shown that a bone marrow-derived population repopulates many tissue niches in the recipients, including the distal and proximal airway (4). In a human study of lung transplantation between donors and recipients of opposite genders, examination of airway biopsies of the transplanted organs for the presence of the Y chromosome showed recipient-

derived airway epithelial cells, type II pneumocytes, and bronchial mucus glands cells, with a greater degree of chimerism in chronically injured epithelia (28). Similar epithelial chimerism had been noted in sex-mismatched haematopoetic stem cell transplantations (36, 37, 39).

Cytokeratins are widely used as markers of epithelial cell differentiation and cytokeratin-5, in particular, is a marker of cells of complex epithelia, including airway epithelia (40). Recently, a bone marrow-derived, CD45+ cytokeratin+ cell was identified in the peripheral blood of both mice and humans and found to populated the proximal airway epithelium in a mouse model of syngeneic sex-mismatched tracheal transplantation (32) and bone marrow transplantation (41–43). In sex-mismatched transplantation of unfractionated bone marrow or bone marrow side-population from ROSA-26 donors to wildtype recipients, 0.83–1.6% of recipient tracheal epithelium was shown to be donor-derived (42, 43), and transplantation of wildtype marrow to CFTR-deficient recipients resulted in similar engraftment of CFTR-expressing cytokeratin+ donor-cells in the airway epithelium (41). In the tracheal transplant model, the recruitment of these cells to the airway was mediated via the CXCR4-CXCL12 chemokine axis: depletion of CXCL12 prevented the normal re-establishment of the normal pseudo-stratified respiratory epithelium, and, remarkably, resulting in epithelial squamous metaplasia derived from resident progenitor cells (32). This observation lends credence to the hypothesis that lung cancer may, in part, be the consequence of dysregulated repair by specific progenitor populations (44, 45).

B. Alveolar epithelium

It is currently controversial whether alveolar epithelial cells can be repopulated from an extra-pulmonary progenitor cell, with reports in the literature reaching conflicting conclusions from different experimental systems. In two studies, unfractionated bone marrow cells or bone marrow stem cells from transgenic donors with ubiquitous expression on eGFP or LacZ (under the control of the β-actin promoter) or donors with type II pneumocyte-expression of eGFP (under the control of the pro-surfactant C promoter) were transplanted into wildtype recipients (46, 47). In these studies, no transgenic cells were found to populate type II alveolar epithelial cells in unchallenged recipients using deconvolution microscopy (46) or in recipient animals with radiation- or bleomycin-induced lung injury using immunofluorescent microscopy (47).

In contrast, when plastic adherent bone marrow cells from donors that ubiquitously express LacZ were delivered intravenously to recipients 5 days after intra-pulmonary challenge with bleomycin, LacZ expression was detected in type I, but not type II, pneumocytes up to 30 days after the cell transfer, using morphologic criteria and expression of T1α and aquaporin-5 to identify type I alveolar epithelial cells (29). Similarly, when wildtype recipients engrafted with GFP bone marrow were challenged with intranasal PBS or LPS, both GFP+ cytokeratin+ CD45− cells with morphologic characteristics of type I pneumocytes, and flat GFP+ CD34+ CD45− cells (representing endothelial cells, discussed below) were detected in alveolar walls of LPS- but not PBS-treated animals (48). A third study showed similar results when the recipient lungs were injured using high-doses of radiation (49). Furthermore, the relevance of these marrow-derived progenitors to lung repair was tested by sublethal irradiation before LPS challenge, which resulted in greater lung damage that could be abrogated with bone marrow transfer (48). In another model system, GFP-transgenic mice were surgically joined to wildtype littermates such that they developed common circulation, and the lungs of the wildtype animals were injured with lethal irradiation with or without elastase. GFP-expressing cells in the lungs of wildtype animals consisted of macrophages, subepithelial fibroblast-like interstitial cells, and type I alveolar epithelial cells (50).

With regard to type II pneumocytes, bone marrow-derived cells were found to engraft 2 to 14% of these cells in a mouse model of sex-mismatched whole bone marrow transplantation and radiation-induced lung injury, using FISH for the Y chromosome and surfactant protein B mRNA (31). Two other groups used sex-mismatched and GFP-expressing bone marrow transplant approach and found rare donor-derived type II epithelial cells in the recipient, as defined by expression of cytokeratin or surfactant protein-B mRNA (51) and CD45-negative pro-surfactant protein-C-expressing cells (52). Similarly, ~2% of type II alveolar epithelial cells in human recipients of sex-mismatched allogeneic haematopoetic cell transplant recipients were found to be derived from the donor (53). In another manuscript, enriched bone marrow mesenchymal stem cells were transferred from male Balb/c mice, which are resistant to bleomycin-induced lung injury, to female C57Bl/6 recipients challenged with intratracheal bleomycin. These investigators found that male cells, as detected by FISH for the Y chromosome, had an epithelial morphology and were enriched 3-fold when the injured lung was selected for type II pneumocytes (54).

Circulating endothelial progenitor cells

Human circulating endothelial progenitor cells are identified as circulating cells expressing CD34, VEGF-R2 and CD133 (55, 56), and since their initial description in 1997 (57), they have been implicated in diverse diseases, including a number of lung diseases.

Several groups have examined the role of these cells in the context pulmonary hypertension, a prototypical pulmonary endothelial disorder: In a rat model of monocrotaline-induced pulmonary hypertension, intravenous administration of either autologous bone marrow endothelial progenitor cells to wildtype animals or human circulating endothelial progenitors to nude rats resulted in engraftment of the cells in the distal pulmonary arteriolar endothelium (58, 59). In the context of a mouse model of hypoxic pulmonary hypertension, circulating endothelial progenitor cells increased in number and incorporated into the pulmonary endothelium in wildtype animals, a sequence of events that was impaired in mice deficient in the erythropoietin receptor (60). Importantly, several groups have investigated the therapeutic potential of exogenously administered endothelial progenitor cells in pulmonary hypertension: administration of normal endothelial progenitor cells resulted in modest reductions in pulmonary pressures in animal models (59, 61); in addition, investigators have used these cells to target the delivery of therapeutic transgenes to the pulmonary vascular endothelium, demonstrating efficacy of delivery of cells transduced with the vasodilators eNOS (58) and adrenomedullin (59) in rat model of monocrotaline-induced pulmonary hypertension. The relevance of this work to human disease was established in a small randomized trial of patients with idiopathic pulmonary arterial hypertension, in which infusion of cultured autologous endothelial progenitor cells was shown to result in improved exercise capacity during standardized 6 minute hall walk as well as haemodynamic parameters (62). More broadly, the number of circulating endothelial progenitor cells have been shown to be reduced in patients with advanced lung diseases, including severe COPD and restrictive lung diseases (63, 64). Although the mechanism of this observation is not clear, one possible explanation for this could involve secondary pulmonary hypertension. Conversely, exposure of neonatal mice to hyperoxia resulted in impaired lung development reminiscent of bronchopulmonary dysplasia, and was associated with decreased number of endothelial progenitors in the bone marrow, blood and lungs (65), leading to the hypothesis that reduced availability of endothelial progenitor cells results in impaired lung angiogenesis and alveolarization in bronchopulmonary dysplasia (66).

Beyond their role in pulmonary hypertension, endothelial progenitor cells have also been studied in the context of several forms of lung injury and inflammation. Specifically, the number of circulating endothelial progenitor cells were noted to be elevated in patients with

bacterial pneumonia (67) and acute lung injury, where reduced numbers of circulating endothelial progenitor cells was associated with worse outcome (68). Similarly, in wildtype mice transplanted with GFP-expressing bone marrow, intrapulmonary administration of porcine pancreatic elastase (69) resulted in mobilization of marrow-derived endothelial progenitors to the blood and their incorporation into the lung capillary endothelium, and similar challenge with intrapulmonary LPS resulted in mobilization of both epithelial and endothelial cells from the bone marrow to the blood and the lung (48). In another manuscript, the number of circulating endothelial progenitors was found to be elevated in human asthma and both acute and chronic models of mouse airway allergy (70). Furthermore the recruitment of these cells to the lung was associated with airway angiogenesis in the context of the mouse models (70), suggesting that circulating endothelial progenitor cells may have a general role in lung diseases characterized by inflammation and angiogenesis.

Circulating progenitors of lung mesenchymal cells

The source of mesenchymal cells of the lung is an important clinical question, since fibrosis and tissue remodeling is central to the pathogenesis of many chronic lung disorders. Lung fibroblasts and myofibroblasts, in particular, were classically thought to be derived exclusively from resident lung fibroblasts. More recently, however, data from human lung transplantation has indicated that fibroblasts can be derived from tissue-resident mesenchymal stem cells (71) as well as a recipient bone marrow-derived precursor cell (72). Similarly, animal models suggest that fibroblasts can differentiate from pulmonary epithelial cells (73) and a bone marrow precursor cell, the fibrocyte (30). Fibrocytes are bone marrow-derived cells with monocytic morphology, that express markers of leukocytes, haematopoetic stem cells, and fibroblasts, but their precise relationship to adult bone marrow mesenchymal stem cells and multipotent adult progenitor cells is yet to be defined.

A. Plasticity of Fibrocytes

Fibrocytes are bone marrow-derived cells that express the haematopoetic stem cell antigen CD34, the common leukocyte marker CD45, the myeloid markers CD11b and CD13, HLA-DR, and several fibroblast markers, including vimentin, collagen I, collagen III, and fibronectin (23, 30, 74). They do not express T cell markers (CD3, CD4, ad CD8), B cell markers (CD19), the IL2 receptor chain CD25, the low affinity Fc gamma receptor III (CD16), myeloid markers (CD14 and nonspecific esterase) (22–24, 30, 74, 75). There is evidence that fibrocytes can differentiate from CD14+ peripheral blood monocytes (76–79). In culture, fibrocytes spontaneously express α-smooth muscle actin and loose expression of CD34 and CD45, and this can be augmented in the presence of TGF-β or endothelin, indicating differentiation into myofibroblasts (22, 24, 30, 74, 75). Similarly, in an in vivo model of skin wound healing, bone marrow transplantation of from GFP-transgenic animals to wildtypes showed that cells in the wound co-expressed GFP and α-smooth muscle actin, indicating the myofibroblasts were derived from the bone marrow (80). Fibrocytes can also differentiate into adipocytes both in vitro and in vivo, via a process that can be inhibited by TGF-β via down-regulation of PPAR-γ (81).

B. Trafficking of Fibrocytes

Cellular traffic from the bone marrow to the circulation and subsequently into peripheral tissues is a complex and multi-step process requiring coordinated adhesion molecule and chemokine ligand-receptor interactions. Similar to conventional leukocytes, this process is beginning to be described in fibrocytes: While no chemokine receptor or receptor combinations exclusively identify fibrocytes, human fibrocytes express the chemokine receptors CCR3, CCR5, CCR7 and CXCR4, while mouse fibrocytes express CCR7, CXCR4

and CCR2 (24, 30, 74, 82). The CXCR4-CXCL12 axis, in particular, is involved in traffic of bone marrow-derived progenitor cell (83). Fibrocytes express CXCR4 and to migrate in response to CXCL12 under specific conditions in vitro and in the context of intra-pulmonary bleomycin challenge in vivo (30, 84). A second, smaller population of fibrocytes expressed CCR7, a receptor well-described for mediating efflux of dendritic cells and T cells from peripheral tissues to lymph nodes (85), in the bleomycin-induced pulmonary fibrosis model, although the intrapulmonary recruitment of $CXCR4^+$ fibrocytes was markedly greater than $CCR7^+$ fibrocytes (30). Similarly CCR2 has been shown to have a role in the recruitment of fibrocytes in a model of FITC induced lung injury and this appears to be mediated by CCL12 (82, 86). Interestingly in a model of renal fibrosis, CCR7 appeared to have an important role in the recruitment of fibrocytes to the kidney (87). Of the CCR7+ fibrocytes in this study, 66.5% were also positive for both CXCR4 and CCR2 expression, and 16.8% were positive only for CXCR4 and negative for CCR2. Moreover, 13.0% of the CCR7 negative fibrocytes were found to be positive for CXCR4 (87). It therefore seems that, at least in mice, fibrocytes can use different chemokine ligand-receptor pairs for tissue homing in the context of different diseases in different organs.

C. Fibrocytes in asthma

Airway remodeling is an important component of asthma pathogenesis, and refers to a diverse set of structural changes, including epithelial metaplasia, subepithelial fibrosis, smooth muscle hyperplasia, and angiogenesis. Fibrosis around the airways, in particular, is a central feature of remodeling, and is thought to be poorly responsive to current treatments of asthma, as recently reviewed (88, 89). Airway biopsies from patients with asthma demonstrate increased numbers of CD34+ and collagen-I+ cells as well as cells co-expressing CD34, CD45RO, and α-SMA as compared to controls, and the number of these cells correlated to the number of fibroblasts that could be isolated from the bronchoalveolar lavage fluid (90). In a model of human asthma allergen challenge, accumulation of CD34+ collagen-I+ and a smaller number of CD34+ α-smooth muscle actin+ cells below the basement membranes, within 24 hours after antigen challenge (22). Cells with the same markers accumulated in the airway walls in mice in the ovalbumin model of lung allergy. In addition, when fibrocytes were isolated from the peripheral blood, labeled, and administered intravenously to allergic mice, they homed to the airway walls and down-regulated CD34 but up-regulated α-smooth muscle actin. Lastly, cultured human CD34+ collagen-I+ cells showed enhanced expression of α-smooth muscle actin in response to enothelin-1 and TGF-β (22).

D. Fibrocytes in interstitial lung diseases

Interstitial lung diseases are a large group of disorders characterized by varying degrees of inflammation and fibrosis of the lung parenchyma. Most are insidious in onset and result in irreversible, and sometimes progressive, replacement of lung tissue with scar. Some interstitial lung diseases are responses to specific environmental exposures, such as inorganic dusts, hypersensitivity to organic molecules, or toxic effects of medications, others are complications of multi-system diseases, such as connective tissue disease, while others still are of unknown aetiology. Among these idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis (IPF) is the most common; it is defined as the histopathologic finding of usual interstitial pneumonia (UIP) in the absence of other recognizable cause of interstitial lung disease. While no animal model completely replicates human IPF, the intrapulmonary administration of bleomycin to mice results in epithelial cell necrosis within 24 hours, acute alveolitis after 2–3 days, and intense interstitial inflammation associated with fibroblast proliferation and extracellular matrix synthesis over the ensuing 2–3 weeks, with gradual resolution of the injury over the subsequent 3 weeks (91, 92). While this model resembles some features of human IPF histologically, it differs from the human disease in that it is

more acute, is self-limited, and is the consequence of a single insult. Despite its shortcomings, the bleomycin model represents the best available and most widely used model for studying human interstitial lung disease.

Several characteristics of fibrocytes might allow them to contribute to the pathogenesis of fibrotic interstitial lung diseases: they can differentiate into fibroblasts and myofibroblasts (22, 24, 30, 74, 75), can generate cytokines that induce collagen deposition (75, 93), produce pro-angiogenic mediators (94), and are potent antigen presenting cells and can recruit and activate T cells (95). In addition, transferring non-leukocyte bone marrow cells to mice in the context of the bleomycin model results in accumulation of these cells in the lung and attenuates the degree of lung injury and fibrosis (26, 54, 96). Similarly, bone marrow-derived progenitor myofibroblasts have also been found in murine radiation-induced fibrosis (25). In contrast, another manuscript compared wildtype mice transplanted with marrow from GFP-transgenic donors 4 weeks after intrapulmonary bleomycin and saline challenge, and found no difference in the proportion of donor-derived lung fibroblasts to total lung fibroblasts between the two groups (97). Importantly, however, the more relevant readout of the absolute number of donor-derived lung fibroblasts was not compared between the two groups in this manuscript.

Regarding the mechanism of recruitment of fibrocytes to the lung, both human and murine peripheral blood fibrocytes have also been shown to traffic to the lungs in response to bleomycin-induced pulmonary fibrosis, and this recruitment correlated with collagen deposition in the lungs (30). Antibody-mediated neutralization of CXCL12 in this model resulted in reduced fibrocyte recruitment to the lung and attenuated lung collagen deposition, thus implicating the CXCL12-CXCR4 axis in this process (30). Another group examined the contribution of fibrocytes to pulmonary fibrosis using a model of intrapulmonary FITC administration (82). In this model, fibrocytes were isolated from both the bronchoalveolar lavage fluid and whole-lung mince samples, and were found to express CCR2, CCR5 and CCR7, in addition to CXCR4 (82). Fibrocytes isolated from the mouse lungs expressed CCR2, migrated towards the CCR2 ligands CCL2 and CCL12, but lost expression of CCR2 in culture. Fibrocyte recruitment was impaired in CCR2-deficient mice challenged with intrapulmonary FITC. Furthermore, wildtype recipients of CCR2−/− bone marrow had reduced recruitment of fibrocytes to the lungs and were protected from pulmonary fibrosis, while recruitment of fibrocytes was restored in CCR2−/− recipients of wildtype bone marrow (82). Surprisingly, these results were not replicated in CCL2-deficient animals, but immunoneutralization of CCL12 resulted in reduced recruitment of fibrocytes to the lung and attenuated pulmonary fibrosis (86). In summary, these results implicate the CCR2-CCL2/CCL12 axis in the FITC-induced pulmonary injury model, although the applicability of these findings to the human disease is tempered by the observation of low CCR2 expression on human fiborocytes and absence of a human homologue for CCL12. Taken together with the CXCL12-CXCR4 data (30), these studies strengthen the case for the importance of chemokine-mediated fibrocyte influx in the pathogenesis of pulmonary fibrosis; the different chemokine axes implicated might reflect differences in the models or, conceivably, serial contingency of fibrocyte recruitment on both CXCL12-CXCR4 and CCR2-CCL2/CCL12 axes.

As noted earlier, expression of chemokine receptors does not, in itself, identify fibrocytes. In one study of surgical lung biopsy samples from patients with idiopathic interstitial pneumonia, CCR7-expressing cells co-expressed CD45 but not CD34, collagen 1, or α-smooth muscle actin, indicating that they were not fibrocytes (98). Expression of CXCR4 in lung fibrocytes has not been demonstrated in human interstitial lung disease to date, but the expression of its ligand, CXCL12 was found to be elevated in both the lungs and plasma of patients with fibrotic interstitial lung disease as compared to healthy controls, and this was

associated with a an order of magnitude increase in the number of peripheral blood CXCR4+ fibrocytes in these patients (38).

Conclusion

Increasing evidence points to a pivotal role of bone marrow-derived progenitor cells contributing both the physiologic lung repair as well as to the pathophysiology of human lung disease. It is likely that the mechanism of recruitment differs between various progenitor cell types and under different physiologic and pathologic conditions; these are yet to be established definitively. In addition, once in the lung, the signaling pathways that govern the differentiation of the progenitor to epithelial or mesenchymal cell type remain to be elucidated. Finally, the relative contribution of bone marrow-derived and resident progenitors under physiologic repair and pathologic fibrosis is yet to be established. A better understanding of these mechanisms has the potential to allow for therapeutic manipulation of regeneration and fibrosis that is observed in most chronic lung diseases.

Key points

- Lung regeneration is a feature of both physiologic recovery from injury and pathologic fibroproliferation.
- Progenitor cells involved in lung repair exist both as resident lung cells and bone marrow-derived progenitors.
- Circulating airway epithelial cell progenitors are CD45+ cytokeratin-5+ cells that home to the airway via the CXCR4-CXCL12 chemokine axis.
- Whether circulating progenitors can repopulate alveolar epithelial calls is controversial.
- Circulating endothelial progenitor cells expressing CD34, VEGFR-2, and CD133, and can repopulate the lung endothelium in experimental models of pulmonary hypertension and several forms of lung injury and inflammation.
- Fibrocytes are circulating mesenchymal progenitor cells that express CD34, CD45 and collagen I, and can give rise to lung fibroblasts and myofibroblasts.
- Fibrocytes have been implicated in the pathogenesis of airway remodeling in asthma and interstitial lung diseases.

Five-year view

We speculate that over the next 5 years, the biology of the various progenitor cells involved in lung repair will become more clear: this includes a better understanding of the lineage of these cells, the mechanism of their release from the bone marrow, adhesion to endothelial surfaces, response to chemokine gradients, and conditions that promote their differentiation into various lung cells. We also anticipate that the role of these cells in other lung diseases will become better defined. Finally, the relative contribution of resident and bone marrow-derived progenitors in the context of physiologic lung repair and pathologic fibroproliferation is likely to become more clear.

Acknowledgments

Sources of funding: This work was supported by NIH grants HL73848 and an American Lung Association Career Investigator Award (Mehrad), AR055075 (Keane), and CA87879 and HL66027 (Strieter).

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