Published in final edited form as:

Chest. 2007 March ; 131(3): 874–879. doi:10.1378/chest.06-2453.

Angiogenesis in Chronic Lung Disease

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Abstract

Chronic lung diseases like COPD, severe progressive pulmonary hypertension (PH), and interstitial lung diseases all have a lung vascular disease component. Cellular and molecular mechanisms of pulmonary vascular remodeling have been experimentally explored in many animal models, and it is now clear that microvessels are involved. In emphysema patients, there is a loss of lung microvessels, and in many forms of severe PH there is obliteration of precapillary arterioles by angioproliferation. Thus, COPD/emphysema and severe angioproliferative PH are on the opposite ends of a spectrum of vascular biology responses. Animal experiments have provided insight regarding some of the initiating events that shape the various forms of pulmonary vascular remodeling. In pulmonary fibrosis and in the postinjury phase of acute lung injury, the angiogenic/angiostatic balance is also affected. This review will therefore discuss angiogenesis in several chronic lung diseases and will speculate on how altered vascular homeostasis may contribute to lung disease development.

Keywords

acute lung injury; angiogenesis; COPD; interstitial lung disease; lung structure maintenance program; pulmonary hypertension

Angiogenesis is a process of vascular development that generates new vessels both during development and also during tumor growth.¹ Angiogenesis that results in the growth of capillaries is distinct from vasculogenesis, which is a process that is prominent in embryogenesis and is involved in the *de novo* generation of vessels. Angiogenesis has not been considered as a topic in discussions of lung diseases until quite recently. Increased angiogenesis occurs in the lungs of patients with idiopathic severe pulmonary hypertension (PH), which is driven to a large extent by the exuberant proliferation of endothelial cells.² On the other end of the spectrum is emphysematous tissue destruction characterized by a loss of the pulmonary capillary bed, which was described many years ago in a landmark article by Liebow.³ As a means of better describing the contribution of angiogenesis to

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The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

normal lung function, this review will briefly discuss the concept of the adult lung structure maintenance program (LSMP).⁴ The broad principle of lung tissue homeostasis as put forth by the LSMP is that structural cells are turning over in the adult lung to replace injured or senescent cells as long as a dense scaffold of matrix proteins exists. With specific respect to angiogenesis, lung vascular homeostasis involves maintaining an ideal number of capillaries per unit of lung volume. Considered in this framework, the response to the activation or injury of vascular cells can result in an imbalanced gain or loss of capillaries, such as in patients with pulmonary hemangiomatosis or severe emphysema, respectively, resulting in progressive chronic disease (Fig 1). This perspective explores the notion that dysregulation of the vascular component of the LSMP is involved in most chronic and progressive lung disorders. The adult LSMP hypothesis was formulated as a conceptual response to the following question: If the adult lung does not actively grow, then is the primary role of vascular endothelial growth factor (VEGF) to maintain lung structure? This concept has recently been reviewed.⁵⁻⁷

Severe Angioproliferative PH

Elevated pulmonary artery pressures in patients with PH have been largely attributed to vasoconstriction. However, in the past 10 years there has been emerging evidence that exuberant angioproliferation is also an important contributor to vascular resistance. Tudor et al² first reported in 1994 that exuberant endothelial cell growth and elements of inflammation were present in PH-associated plexiform lesions. As evidence for a process of disordered angiogenesis, Tudor and coworkers² demonstrated the expression of angiogenesis-related molecules in the plexiform lesions of patients with severe pulmonary arterial hypertension.⁸ Cells from plexiform lesions express VEGF messenger RNA and protein, and overexpress both messenger RNA and the protein of VEGFR-2 and the transcription factors hypoxia-inducible factor (HIF)-1 α and HIF-1 β . In patients with idiopathic pulmonary arterial hypertension, some of the plexiform lesion vascular endothelial cells (ECs) grow monoclonally,⁹ and these ECs display somatic cell mutations.¹⁰ The ECs making up the complex vascular lesions are phenotypically abnormal with the loss of several tumor suppressor genes¹¹; there is a paucity of apoptotic cells in these lesions.¹¹ Thus, in many forms of severe PH, an exuberant proliferation of vascular ECs may contribute to disease development.

Airspace Enlargement/ Emphysema

In contrast to many forms of PH that are characterized by increased angiogenesis, emphysema is remarkable for a relative paucity of blood vessels. COPD patients have a significantly reduced capillary length and length density.¹² VEGF receptor blockade in an experimental emphysema model of COPD¹³ induced the loss of microvessels and was associated with alveolar septal cell apoptosis and airspace enlargement. This result suggests that a normal alveolar structure is not maintained without capillary ECs, and that the ensuing lung cell apoptosis culminates in emphysema.¹⁴ Several groups have reported that in cases of human emphysema there is an increase in detectable lung septal cell apoptosis.^{15,16} Additionally, Morimoto et al¹⁷ reported impaired phagocytic removal of apoptosed cells in BAL fluid samples from COPD patients. Thus, it appears that one consequence of lung cell

apoptosis is a failure of angiogenic repair. The loss of microvessels may also be a cause of the muscle-wasting component of end-stage COPD.¹⁸ Thus, the association with blood vessel paucity (or absent angiogenesis) is consistent with the hypothesis that vascular regression is another facet of lost vascular homeostasis, which is ultimately involved with the lung parenchymal and muscle loss observed in emphysema patients.

Asthma

Angiogenesis has only been appreciated in more recent years as an important contributor to airway remodeling in patients with bronchial asthma. Engorgement of dilated and remodeled vessels is a consistent feature in the airways of patients with fatal asthma.¹⁹ Both adults^{20,21} and children²² with mild-to-moderate asthma have an increased number of subepithelial bronchial vessels compared with non-asthmatic subjects, suggesting that angiogenesis is potentially a central component in the progression of airway remodeling. Increased airway vascular density associated with increased VEGF gene expression has recently been reported²³ in a primate model of chronic asthma. Whether angiogenesis is secondary to or independent of chronic airway inflammation has not been conclusively determined. However, biopsy specimens from steroid-treated adult asthmatic patients with moderate-to-severe disease had consistently higher subepithelial vessel densities than those from patients with mild disease,²¹ indicating that vascular remodeling may be driven by inflammation-independent proangiogenic signals in patients with chronic asthma.

Pulmonary Fibrosis

Although it has been acknowledged that some patients with interstitial lung disease have a pulmonary vascular disease component, usually characterized by the muscularization of small arteries, relatively little attention has been paid to the microvasculature. Cosgrove et al²⁴ examined lung tissue samples obtained from patients with interstitial lung disease. They examined histochemically the vascular density in the fibroblastic foci and found that the vessel density was decreased in association with a high expression of the angiostatic pigment epithelium-derived factor protein, which colocalized with smooth muscle actin. Keane et al²⁵ demonstrated angiogenic activity in a large number of lung samples with idiopathic pulmonary fibrosis, and Ebina et al²⁶ found both increased capillary density and vascular regression in the same lung at different sites, raising the question of whether angiogenesis is part of the fibrotic program or part of an antifibrotic “strategy” of the lung. Presently, the question of whether vascular remodeling is central or peripheral to the development of pulmonary fibrosis is an open question.²⁷

Angiogenesis and Repair in Late-Phase Acute Lung Injury

The aftermath of acute lung injury (ALI)/ARDS is typically characterized by the resolution of inflammation by apoptosis and phagocytic clearance of dead cells, and epithelial and endothelial proliferation with the reestablishment of a functional gas-exchanging alveolar-capillary interface. Hyperactivation of the LSMP, however, may account for the progression to fibroproliferative ARDS with progressive intraalveolar and intraseptal angiofibroproliferation.²⁸ The result is chronic lung disease that is characterized by persistent interstitial fibrosis and pulmonary vascular dysfunction.²⁹ The angiographic

appearance is that of pulmonary microvascular involution³⁰ with subpleural “picket-fencing” associated with the development of secondary PH (Fig 2).³¹ In survivors of ALI/ARDS, lung volumes and airflow deficits generally normalize by 12 months. However, deficits in the diffusing capacity of the lung for carbon monoxide (a surrogate for persistent alveolar-capillary dysfunction) generally persist, and correlate with impaired effort tolerance and performance status.²⁹ Angiogenic repair is thus an important mechanism in reestablishing a functional gas-exchange interface.

The effective clearance of apoptotic cells sets the stage for the resolution of unchecked inflammation.^{17,32,33} The clearance of apoptotic cells, either by professional phagocytes (*eg*, alveolar macrophages) or by regenerating alveolar epithelial cells, results in paracrine secretion of antiinflammatory and potentially angiogenic and profibrotic chemokines and growth factors.³³ The loss of alveolar airspace/intravascular partitioning of VEGF is characteristic of ALI.^{34,35} Significant increases in circulating VEGF levels are associated with the loss of endothelial tight junction integrity and result in significant reductions of alveolar epithelial lining fluid concentrations. VEGF is both a vascular permeability factor as well as a potent regulator of angiogenesis, and is tightly regulated at a transcriptional level by HIF-1 α in response to hypoxia (reviewed in the article by Hirota and Semenza³⁶) as well as proinflammatory environments, including the lung.³⁷ The resolution of inflammation and the initiation of endothelial and epithelial repair is heralded by phagocytic clearance of apoptotic cells (resulting in VEGF secretion) and type 2 alveolar epithelial cell proliferation that is regulated in part by β -catenin activation,³⁸ resulting in reconstitution of the alveolar-capillary interface. Exuberant repair, characterized by fibroangiogenic proliferation, can, however, result in septal matrix turnover and lung remodeling that may progress to chronic fibrotic lung disease and persistent respiratory insufficiency.³⁹

In addition to VEGF, several other angiogenic regulators have been identified as critical to the progression of ALI and the reestablishment of the function of the pulmonary microvasculature in patients with ALI. Proangiogenic Glu-Leu-Arg motif containing CXC chemokine ligands 5, 1, and 8, and their common CXC chemokine receptor 2 have also been implicated as important regulators of angiogenesis in patients with ALI.⁴⁰

Angiopoietin (Ang)-1 and Ang-2 are competitive antagonists for the Tie-2 receptor that is highly expressed on endothelial cells and microvascular pericytes. Ang-2 is thought to act as a microvascular destabilizer in low-VEGF microenvironments with resultant endothelial involution and regression (reviewed in the article by Thurston⁴¹). Ang-2 has been shown to independently regulate pulmonary vascular leakage during the exudative phase of ALI in humans with sepsis-associated ALI, and its effects are mitigated by Ang-1.⁴²

The resolution of ALI is characterized by the significant turnover of septal matrix with the activation of both serine metalloproteinase and matrix deposition, which mediate fibrogenesis. Associated with this is the elaboration and expression of adhesion molecules, key among which are Arg-Gly-Asp motif peptide molecules such as fibronectin and α V β 6 that signal for endothelial proliferation growth.^{43,44} Several counterregulatory molecules such as tissue inhibitor of metalloproteinase-1 and the collagen XIII degradation products angiotatin and endostatin are also elaborated, and contribute to epithelial injury and

potentially impair normal angiogenic repair and remodeling.⁴⁵ Thus, the matrix microenvironment regulates the balance between proangiogenic and antiangiogenic signals in the postacute phase and contributes to angiogenic remodeling.

Several lines of evidence from animal models and humans indicate that regeneration of the denuded pulmonary microvascular endothelium after ARDS is achieved both by mobilization of bone marrow-derived endothelial cell progenitors and potentially from resident lung side-population stem cells, which is a less well-characterized pool.⁴⁶ Circulating endothelial progenitors are associated with increased survival in ARDS patients.⁴⁷ The extent of microvascular engraftment is thought to depend on the integrity of the “biological” scaffold of the damaged lung (*ie*, the microenvironmental milieu of growth factors including VEGF and glycosylated basement membrane proteins onto which circulating progenitors can engraft). Poor progenitor engraftment may result from extensive architectural remodeling and fibrosis, thus depleting the lung of potential microniches for engraftment and facilitating the progression of pulmonary vascular dysfunction in ARDS survivors. Pluripotent side-population cells expand in response to ALI but may be extensively damaged and be a less important source for angiogenic repair.

Conclusions

Angiogenesis is a fundamental principle of vascular remodeling and repair. However, the association of pulmonary vascular cell apoptosis as an initiating mechanism for angiogenesis in chronic lung disorders has not been widely appreciated. This review has described in a broad fashion how disordered angiogenesis may be implicated in the disease pathogenesis of PH, emphysema, asthma, pulmonary fibrosis, and late-phase ARDS, and in regulation of the progression to chronic lung disease. An emerging understanding of the mechanisms governing the angiogenic/angiostatic balance in patients with chronic lung diseases should facilitate the development of highly targeted therapies. As an example, agents that specifically induce apoptosis in abnormal, lumen-obliterating ECs in patients with severe pulmonary arterial hypertension⁴⁸ provide an encouraging potential therapeutic avenue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

ALI	acute lung injury
Ang	angiopoietin
EC	endothelial cell
HIF	hypoxia-inducible factor
LSMP	lung structure maintenance program
PH	pulmonary hypertension
VEGF	vascular endothelial growth factor

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Figure 1.

Effective and ineffective angiogenesis in the pathogenesis of chronic lung diseases. Loss of homeostatic control of vascular integrity in the face of activation or injury of the pulmonary vasculature (*eg*, oxidant stress injury) modified by host and environmental factors initiates apoptotic cell death. Optimally, the reestablishment of the alveolar-capillary membrane results in normal lung repair. Hyperactivation results in exuberant proliferative angiogenesis (*ie*, PH, late-phase ALI/ARDS, and asthma). By contrast, the failure of angiogenic repair can result in septal involution and airspace dilatation as part of emphysema.

Figure 2.

Postmortem pulmonary angiograms demonstrating angiogenic regression and remodeling in an patient with ALI/ARDS. At 16 days after initial aspiration injury (*left, A*), there is marked vascular obstruction and splaying of the septae. The normal reticular appearance of subpleural vessels is distorted with a picket-fence appearance (arrows) as a result of septal deformation, airspace dilatation, and early fibrosis. By 26 days (*right, B*), angiogenic remodeling with fine “hazy” new vessels (arrowheads) are apparent between dilated and tortuous pulmonary vessels and cystic airspaces. Reprinted from Tomashefski et al³⁰ with permission.