HIGHLIGHTED TOPIC | Lung Growth and Repair

Vascular remodeling in the circulations of the lung

Wayne Mitzner and Elizabeth M. Wagner
Departments of Environmental Health Science and Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland 21205
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Mitzner, Wayne, and Elizabeth M. Wagner. Vascular remodeling in the circulations of the lung. J Appl Physiol 97: 1999–2004, 2004; doi:10.1152/japplphysiol.00473.2004.—The lung is unique in its double sources of perfusion from the pulmonary and systemic circulations. One striking difference between the two circulations is the capacity for angiogenesis. The bronchial circulation has a capacity that seems quite similar to all systemic arteries, whereas the pulmonary circulation seems relatively inert in this regard. Extra-alveolar pulmonary arteries can grow somewhat in length, and septal capillaries seem to have the capability of reforming, but these processes do not seem to occur with nearly the same intensity associated with the bronchial arteries. In this review, we emphasize these differences between the two circulations of the lung, anticipating that future research will allow more focused probing into the molecular signaling that regulates the novel mechanistic and pathological pathways of each.

bronchial circulation; angiogenesis; pulmonary

IN THIS REVIEW, WE WILL USE the term remodeling to mean changes in the structure of blood vessels associated with growth into new or existing tissues. This growth may be associated with many pathological processes, including changes in endothelial cell proliferation, smooth muscle properties, barrier function, tumor vasculature, and a host of accessory cells. Such changes may or may not influence function, and they may not be acutely reversible. A comment to clarify semantics is warranted before getting too much further into the discussion. Several terms have been used to identify this remodeling, including angiogenesis, arteriogenesis (54), vasculogenesis (20, 57), and neovascularization (9), and are often applied to new blood vessels. Although there may be different processes associated with each of these terms, our focus will be more on the common aspects of remodeling. There has been, however, a recent emphasis on distinguishing vasculogenesis from angiogenesis. Angiogenesis refers to new vessel growth that originates from an existing vessel, and vasculogenesis refers to new vessels that originate independently of existing vessels (20, 57). For the purpose of efficient fetal lung development, these processes need to go on in a coordinated fashion. Indeed, what good would angiogenic pulmonary arteries be if there were no capillary and venous system to hook up with? Thus, where true vasculogenesis occurs in lung development, it must be followed up within a very short time by some connection to the existing circulation. Although the definition of these terms by themselves makes logical sense and may be useful in separating the signaling pathways associated with vascular modeling and remodeling during development, this distinct partitioning is less clear in vascular remodeling in adult lungs. For example, when the pulmonary artery of mature lungs is obstructed, rapid and extensive growth of the bronchial circulation occurs in all mammalian species larger than the mouse (see discussion in DEVELOPMENT OF THE BRONCHIAL VASCULATURE). Although hypoxia is often listed as a stimulus for angiogenesis, the fact that angiogenesis readily occurs in the ventilated lung with obstruction of deoxygenated pulmonary blood flow proves that ischemia is the more relevant stimulus. In this situation, ischemic lung tissue sends signals that are somehow transmitted first to nearby small existing vessels and then to the larger arteries to begin to grow to meet this need. Independent vasculogenesis may not be easily separated in such cases. However, in a mouse model of pulmonary obstruction (44), where there is no bronchial circulation, in the lung parenchyma adjacent to where new systemic vessels will eventually develop across the pleura, there appear enlarged vascular pools a few days after artery ligation (unpublished observations). Although these structures may appear similar to vasculogenesis, the fact that such vascular pools only appear near to where the pleura will eventually be breached suggests that their formation is not an independent process. Rather, it is directed or regulated by signals from across the pleura. A similar situation is obtained when a lung tumor grows beyond the point where it can be nourished by the existing pulmonary circulation. At such time, the cancerous tissue becomes ischemic and starts signaling nearby pulmonary and systemic vessels a need for increased perfusion. Initially, this leads to remodeling at the level of the microcirculation of bronchial of pulmonary capillaries, which then must draw increased flow from the larger vessels (31).
This process occurs to a lesser extent in chronic asthma, where there is often a slight thickening of the airway wall, accompanied by increased smooth muscle and vascularization (39).

Methods and end points to assess vascular remodeling are quite variable and are beyond the scope of this review. We also will be less concerned with how to separate vascular remodeling from vascular modeling, i.e., from those processes that occur with normal development. For example, what differences might there be between the growth of the bronchial circulation with pulmonary artery obstruction and the growth of this same circulation during development? There are clearly different processes and signaling occurring with pathological hypertrophy of vessels, but when new vessels grow in mature lungs, they likely employ many similar processes as occur during development. Because the lung does contain these two distinct and unique vascular beds with different responses to specific lung perturbations and pathologies, we consider each circulation separately in this review.

**DEVELOPMENT OF THE PULMONARY VASCULATURE**

In humans, the pulmonary venous system develops at about the same time as that of the pulmonary arterial system. Around the seventh to eighth week of gestation, pulmonary arteries are developed and are connected with the pulmonary arch (14, 25). At about the same time, there are also large patent pulmonary veins in communication with the left heart (20), and this connection to the heart precedes that of the pulmonary arteries. Of course, because there is no need for pulmonary arterial blood flow in fetal life, there is no immediate need for the pulmonary arteries to develop a patent lumen. Once they leave the hilum, the pulmonary veins in humans run independently from the arteries that always accompany the airway tree, but in most other mammals the pulmonary veins also run in concert with the airway tree. In the physiological literature, these vascular trees are referred to as extra-alveolar vessels to distinguish them from the alveolar septal vessels that are sub-vascular trees are referred to as extra-alveolar vessels to distinguish them from the alveolar septal vessels that are sub-

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**REMODELING OF THE PULMONARY VASCULATURE**

The pulmonary vasculature seems to have much more limited capacity for angiogenesis than the bronchial vasculature (62). However, there are several situations where some remodeling manifests itself, including lung cancer and pneumonectomy.

**Lung cancer.** Angiogenesis in lung tumors is necessary if the tumor is to grow to any substantial mass beyond that which can be supplied by simple diffusion from the existing circulation. Although the blood flow that supplies lung tumors can theoretically arise from either the pulmonary or systemic circulations, there is general agreement implicating the systemic circulation in the lung as the initiator of the blood supply to primary lung tumors (31, 43, 45). As already noted, the bronchial circulation has a prolific capacity for angiogenesis. In the process of this vascular growth, new arterial anastomoses often form between the bronchial and pulmonary circulations. These anastomoses allow the pulmonary vasculature to supply nutrient flow to the tumor even if the systemic sources are embolized (45). The pulmonary vasculature can thus function as a maintenance vasculature for lung tumors, but with little apparent capacity for angiogenesis, the systemic vasculature provides the primary source for new vessel growth. Although this schema applies to primary lung tumors, the vascular supply for metastatic lung tumors is more variable, and although there is radiographic evidence for angiogenesis in the pulmonary circulation that supplies these tumors (43), such evidence in pulmonary blood vessels of developed lungs is quite rare. The process that occurs in these secondary tumors may be similar to what occurs after pneumonectomy (PNX) in mature animals, when one lung enlarges and grows into the space previously occupied by the excised lung (49).

**Pneumonectomy.** When a lung is excised, compensatory lung growth normally occurs in the remaining lung. The stimulus for this growth seems to be the increased inflation stress caused by the lung removal. Thus there is a bigger effect on left lung volume after right PNX than vice versa (29, 30), presumably because the thoracic inflation stresses are greater when a larger lung is removed. Although there have been many studies of the responses of the remaining lung to PNX, relatively few have looked closely at the changes in the remaining pulmonary vasculature. One presumes that the increased alveolarization that occurs after PNX is associated with functional
septal capillaries, but this is not certain. Furthermore, how this new microcirculation within alveolar walls might be serviced by arteries and veins is even less well documented. To the extent that there is lengthening of the airway tree (16), then it seems reasonable to presume that the pulmonary arteries that accompany the airways must also lengthen. Although there have been few studies that have examined changes in the pulmonary venous structure after PNX, one must also assume that if the remodeled alveoli are being perfused by the pulmonary arteries, then the pulmonary veins must also be remodeled. In mammals where the arteries and veins accompany the airways, this process can be visualized. However, in humans or dogs, where the pulmonary veins run independently from the airway tree, it is less easy to picture.

Davies et al. (18) have shown that 5 yr after a left PNX, the right lung expands to fill the left space with both alveolar enlargement and number. The precartilaginous pulmonary arteries in dogs operated on at 1 yr of age showed increased smooth muscle and medial hypertrophy in all arteries. This vascular hypertrophy and the presumed increase in vascular lengths likely explain the increased pulmonary artery pressure and increased pulmonary vascular resistance often observed (41, 49). This post-PNX observation of pulmonary remodeling leading to hypertension, however, is subject to considerable variability within and among species (18, 66), and thus it remains an unsettled issue.

Somewhat related to PNX is the issue of lung transplantation. One clinical concern in such cases is what happens when the transplanted lung does not fit precisely the recipient thorax. Might this be analogous to PNX when the transplanted lung is too small? A similar increased inflation stress would likely operate on the newly transplanted lung. In support of this are experiments where a small immature lung was transplanted into a mature thorax after lung excision. In such case, the transplanted lung was shown to undergo continued lung development to fit the new thorax (27). Both lung and alveolar size after transplantation were of normal appearance. In this work, there was no effort made to assess the vascular structure, but because the airway and alveolar structures seemed to develop normally, one may presume that the vasculature remodeling simply followed a normal developmental pattern.

Role of diet in vascular remodeling. It has been well documented for many years that calorie restriction leads to loss of alveoli and an emphysematous-like lung (50, 51). Despite this knowledge of the effect of such dietary limitations on the lung, the molecular mechanisms underlying this alteration in lung parenchyma have remained obscure. A recent paper by Massaro et al. (40) documents changes in genetic signaling following such calorie restriction in mature mice. Although this paper did identify several acute molecular changes that occur in the destruction process, in particular, granzymes A and B, several caspases, TNF ligands and receptors, and other proteins from cytotoxic lymphocytes and natural killer cells, there was little information on how the capillary vasculature might remodel during the loss of alveoli. Somewhat more controversial, but no less remarkable, is evidence that shows that refeeding can restore alveoli. Such observations raise many questions about the structure of the new alveoli and whether their septal capillaries are fully developed and functional. However, because it is clear that septal capillaries in developed lung have the capability of undergoing substantial growth and remodeling (53), this may be an essential feature of the restoration of alveoli. If it is assumed that this is the situation, this raises the question of how such a complex structure can be reformed in mature lungs. It seems clear that there must be an important interaction of alveolar walls with pulmonary vascular growth as alveoli remodel. For this reason, it is perhaps surprising that Massaro et al. did not find any alteration of VEGF signaling. Nevertheless, there is additional evidence showing that VEGF does play an important role in alveolar formation in young mice (33, 60). This work has clearly shown that transient inhibition of VEGF in early postnatal life leads to an emphysematous adult lung. However, the work still leaves open the question of whether the vasculature drives alveolar formation or vice-versa or whether the process requires a tightly correlated regulation of both.

DEVELOPMENT OF THE BRONCHIAL VASCULARITY

Development of the bronchial vascular network during lung maturation has not been studied extensively. During human vascular development, between the 9th and 12th wk of gestation, the bronchial artery arises as an outgrowth from the aorta, a somewhat later process than pulmonary vascular development (5, 24). One or two vessels extend from the dorsal aorta and form along the cartilaginous plates of the large airways. The vessels extend longitudinally along the airways to the lung periphery as far as the terminal bronchioles. It appears that this vasculature forms as an outgrowth of the aorta, and the process of angiogenesis most aptly applies. However, the process by which the extensive mucosal plexus, as well as the adventitial plexus external to airway smooth muscle, develops is unstudied. Whether the fine capillary network within the airway wall, large pulmonary vessel walls (vasa vasorum), or vessels anastomosing with pulmonary vessels form as a continual outgrowth of arterial sprouting or as de novo formation from mesoderm is unknown.

Inflammation. Inflammation can contribute significantly to bronchial vascular remodeling and life-threatening hemoptysis. Hemoptysis in the vast majority of patients originates from the systemic, rather than the pulmonary vasculature, and the bronchial vessels are almost universally involved (37, 46). Yet, the etiology of hemoptysis requiring therapeutic embolization is variable, and the pathology of bronchial vessels leading to this acute condition is poorly understood. However, several studies have focused on the chronic inflammation of asthma and airway vascular remodeling. Li and Wilson (39) demonstrated increased vascular density in biopsy specimens of subjects with mild asthma compared with normal control volunteers. However, Chu and colleagues (13) showed that only biopsy specimens from asthmatic subjects with concurrent *Mycoplasma pneumoniae* infections demonstrated significantly increased vessel numbers. In addition, Kuwano et al. (38) demonstrated that increased numbers of vessels in asthmatic subjects were proportional to the overall increase in airway wall area. Thus accounting for ongoing tissue remodeling may be important to confirm actual changes in vascular density. To study more completely alterations in airway vasculature in models of inflammation, rodent models have shown increased vessel numbers, size, and permeability characteristics. Airway remodeling after *Mycoplasma pulmonis* infection shows strain-dependent changes in tracheal vascularity in mice (59). Phenotypic
changes in C57BL/6 mice showed increased numbers of tracheal vessels, whereas C3H mice showed increased vessel diameters. These sustained alterations in the tracheal vasculature could be reversed with corticosteroid treatment (58). Additionally, tracheal vessels in rats exposed to M. pulmonis demonstrated a significantly increased permeability in the airway vasculature when challenged with substance P after inflammation was induced (15). Whether these changes also occur in lower airways is predicted, however, not confirmed, and the mechanisms responsible for airway vascular remodeling requires further study.

Systemic vascular responses to pulmonary artery obstruction. Perhaps the most extensively studied form of systemic vascular proliferation within the lung is that which occurs after pulmonary artery embolization. Virchow (61), in 1847, recognized that the bronchial circulation could proliferate and sustain lung tissue distal to a pulmonary embolism. Bronchial arteriograms in patients with chronic thromboembolic disease demonstrate the unique capacity of systemic vessels to proliferate and to invade the ischemic lung parenchyma. Both a dilated bronchial artery as well as a fine meshwork of vessels distal to the pulmonary occlusion can be seen (21). In addition to bronchial neovascularization, several intercostal arteries have been shown also to participate in the neovascularization of the ischemic lung (37). Neovascularization of the systemic circulation into the lung after pulmonary artery obstruction has been confirmed and studied in humans (32), sheep (11), dogs (42), pigs (22), guinea pigs (55), and rats (65). In these models, the importance of the bronchial circulation in supporting the ischemic parenchymal tissue has been confirmed, and both the morphology and physiology of the new vasculature have been studied. Systemic blood flow to the lung has been shown to increase to as much as 30% of the original pulmonary blood flow after pulmonary artery occlusion (42). To further explore the mechanisms responsible for neovascularization after pulmonary embolism, our laboratory established a new model of pulmonary artery obstruction in the mouse (44). Although the bronchial vasculature extends from the carina to the terminal bronchioles in most species (19), our laboratory has shown that mice do not have a functional bronchial vasculature beyond the mainstem bronchi. After left pulmonary artery ligation in the mouse, intercostal arteries provided a source for new vascularization of the lung. Casting the new vasculature demonstrated that intercostal arteries in proximity to the ischemic lung developed a dense vascular plexus that bridged the pleural space and invaded the lung parenchyma. Subsequent work exploring the mechanisms responsible for angiogenesis in this model demonstrated that both lung ischemia and systemic wound healing (thoracotomy) in immediate proximity to the ischemic lung were essential for neovascularization. Furthermore, the ELR +,C-X-C chemokines appear to play a role in the generation of new vessels to the lung (56). With the use of gene array profiling, real time RT-PCR, and protein confirmation, a significant increase in the three C-X-C chemokines macrophage inflammatory protein-2, keratinocyte-derived chemokine, and lipopolysaccharide-inducible C-X-C in the left upper lung (angiogenic) relative to the left lower lung (ischemic) early after pulmonary artery ligation (4 h to 3 days) was demonstrated. This observation adds further support to a growing body of evidence reported by Strieter and colleagues in several lung pathologies that the ELR +,C-X-C chemokines and their G protein-coupled receptor CXCR2 are important proangiogenic factors within the lung. Notably, in studies of non-small cell lung cancer (2, 3, 36) and idiopathic pulmonary fibrosis (34, 35), the ELR +,C-X-C chemokines have been shown to be proangiogenic and the ELR −,C-X-C chemokines provide angiostatic properties.

Effect of hypoxia on the bronchial circulation. Although the bronchial vasculature has been shown to dilate acutely during hypoxic ventilation (4, 63), its proliferative capacity during chronic hypoxia has not been established. Clinically, bronchial vessels appear not to proliferate during primary pulmonary hypertension (21). However, a recent study demonstrated proliferation of the pulmonary vasa vasorum in a neonate exposed to chronic hypoxia (17). The vasa vasorum of large pulmonary vessels are perfused from branches of bronchial arteries (12, 47) and provide nutrient flow to pulmonary arteries and pulmonary veins. Heistad and Armstrong (23) proposed that blood vessels that transport venous blood, such as the systemic veins and the pulmonary artery, depend more on the network of vasa vasorum than on luminal oxygen to support metabolism. Although a paucity of information exists concerning the regulation of pulmonary vasa vasorum, this vasculature has been proposed to account for the modulating influence of the bronchial vasculature on pulmonary vascular barrier properties during ischemia (48). Thus the more recent data of Davie and colleagues (17) demonstrating a marked increase in the vascular density of the pulmonary artery adventitial vasa vasorum provides important new insight regarding the interaction between pulmonary and systemic vascular remodeling. Furthermore, these investigators confirmed that chronic hypoxia resulted in an increase in circulating bone marrow-derived progenitor cells (c-KIT + cells), which also were incorporated into the new vasa vasorum within the wall of the pulmonary artery. Thus this suggests that blood-borne progenitor cells to be delivered to the site of neovascularization may be required for this remodeling process.

REMODELING OF VENOUS DRAINAGE: THE PULMONARY VEINS

Although the pulmonary veins provide the common drainage pathway for both the pulmonary and bronchial circulations, they seem the forgotten sister with regard to knowledge about their capacity for vascular remodeling. This is in stark contrast to the systemic vasculature, where the veins are known for a prolific capacity to remodel. This is clearly evidenced by the frequent removal of large leg veins for cardiovascular surgery, with rapid accommodation and little loss of vascular function. Close to the lung, the systemic venules that drain the tracheal circulation have also been shown to undergo remodeling after inflammatory stimuli (15). However, in the lung parenchyma, there is very little discussion about pulmonary venous remodeling. In lung development, there have been anatomic studies that document the time course of formation of the pulmonary venous tree (20, 26), but once the lung has completed development, there has been little documentation of remodeling of the pulmonary venous tree in the parenchyma. Do these veins have stunted capacity for remodeling like the pulmonary arteries? Although there are true systemic veins that drain the large airways (10), once the airways enter the parenchyma, all of the bronchial venous drainage is into the pulmonary veins.
This drainage occurs at a local level (64); that is, the venous drainage does not flow down the airway tree with the bronchial artery. Rather, drainage occurs via local pulmonary venules and then to larger veins into the left heart. In the hyperplasia of the bronchial circulation after pulmonary artery obstruction, there is likely substantial remodeling of this venular drainage to accommodate what may be as much as a tenfold increase in flow (42). Because even a tenfold increase in bronchial flow is still much less than a normal preobstruction pulmonary venous flow, there would not likely be much change in the larger pulmonary veins. However, the small venules draining the bronchi that connect with these larger veins must undergo substantial remodeling. There may also be some connection with new anastomoses to pulmonary arterioles that then drain through alveolar vessels. It is not known how this remodeling is accomplished, nor even whether these remodeled venules have normal permeability. This could be important, because it has been shown that remodeled venules in the tracheal wall following inflammation are indeed significantly more leaky (15). Similarly, little is known about how the pulmonary venous tree remolds after PNX or with lung cancer. The importance of such remodeling in the veins remains to be shown, but given the fact that the pulmonary veins have the capacity to narrow substantially (1, 52) coupled with the fact that they are downstream from potentially leaky vessels, the impact of such remodeling on lung pathology may be quite important.

SUMMARY

The lung is unique in its double sources of perfusion. One striking difference between the two circulations is the capacity for angiogenesis. The bronchial circulation has a capacity that is accomplished, nor even whether these remodeled venules have normal permeability. This could be important, because it has been shown that remodeled venules in the tracheal wall following inflammation are indeed significantly more leaky (15). Similarly, little is known about how the pulmonary venous tree remolds after PNX or with lung cancer. The importance of such remodeling in the veins remains to be shown, but given the fact that the pulmonary veins have the capacity to narrow substantially (1, 52) coupled with the fact that they are downstream from potentially leaky vessels, the impact of such remodeling on lung pathology may be quite important.

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