Lung neovascularization: a tale of two circulations

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The mammalian vasculature develops by a process called vasculogenesis in which the differentiation and proliferation of endothelial precursor cells leads to formation of tubes that comprise the primary vascular plexus. Subsequent remodeling of the primary vascular plexus by a process called angiogenesis leads to the formation of the highly branched hierarchical vascular tree consisting of arteries, arterioles, capillaries, venules, and veins. A large literature attests to the fact that in organ systems, angiogenesis continues to be an important process for adding new vessels to the mature vasculature. For example, tissue remodeling associated with tumor growth, mechanical stress, and inflammation leads to release of specific growth factors, such as vascular endothelial growth factor (VEGF), that drive angiogenesis to meet organ demands for increased blood supply.

Vascular occlusion studies in the coronary and peripheral vascular beds indicate the presence of a third type of neovascularization response called arteriogenesis. In this process, occlusion of a major nutrient artery induces growth of collateral vessels that originate proximal to the occlusion, spanning the site of obstruction and reestablishing flow to distal regions (3). As different from angiogenesis, which is characterized by capillary sprouting, arteriogenesis, as the name implies, involves formation of new arteries directly from preexisting arteries. The process seems to be driven by the mechanical effects of redirecting high-shear blood flow from vascular sites proximal to the occlusion to surrounding anastomoses.

In the lung, neovascularization responses are complex. The lung is supplied by two circulatory systems, the pulmonary and the bronchial. The pulmonary circulation is a low-shear, high-flow system that is mainly designed to support blood oxygenation, with secondary nutrient and liquid exchange functions in the parenchyma. The bronchial circulation, which is of systemic origin, constitutes less than 1% of the lung’s blood flow and does not participate in blood oxygenation. However, it is the main nutrient and O_2 supply for the airways. The pulmonary circulation arises from the right ventricle, whereas the bronchial circulation arises from the aorta. These separate origins ensure functional separation between the two vascular beds. However, at their outflow ends, the systems merge such that the bronchial flow leaves the lung through the pulmonary venous network.

The understanding of the roles played by these two vascular systems in lung neovascularization has been approached through the response to pulmonary artery occlusion, a procedure that blocks blood flow in the pulmonary, but not the bronchial, circulation. Since the original observations of Virchow (15, 16), numerous reports have documented the lung’s peculiar response to pulmonary artery ligation, in which neovascular expansion occurs specifically in the systemic bronchial supply (2, 5, 6, 18). Not only does the pulmonary circulation not take part in this neovascularization, but under some conditions, pulmonary vessels might actually regress. Thus monocrotaline treatment, which induces pulmonary artery hypertension through the formation of occlusive structures in pulmonary arterioles, causes loss, not formation, of pulmonary vessels (4).

In a classic study, Weibel (18) documented the lung’s neovascularization response to left pulmonary artery ligation in the rat. After the fifth postligation day, proliferative changes were evident in the endothelium, and media of bronchial arteries followed within a month by well-established bronchial arteriogenesis in the lung parenchyma. Weibel noted that the systemic arteriogenesis also originated from vascular systems other than the bronchial, including for example the internal mammary artery. More recent studies from Wagner’s group have substantiated this cross-pleural arteriogenesis response in the lung (11, 17). These authors showed that in mice, pulmonary artery ligation elicits lung neovascularization by vessel ingrowth from intercostal arteries. This remarkable arteriogenesis, in which chest wall vessels cross the pleural barrier and invade the lung parenchyma, is probably attributable to the fact that mice do not have a bronchial circulation. Therefore, the ischemic mouse lung relies on the nearest systemic blood supply, namely that of the chest wall, to provide vascular collaterals. These studies together with reports of lung collateral vessel growth in diseases including fibrosis (14), tumor growth (12), thrombo-embolic disease (13), and pulmonary atresia (10) provide extensive evidence that in many instances, the lung’s neovascularization response is borne by the systemic, not the pulmonary vascular system.

Despite this evidence, the enigma is that considerable evidence also documents the potent angiogenic ability of the mature pulmonary circulation. Several reports indicate that pulmonary vascular angiogenesis tends to be associated with conditions causing alveolar proliferation. For example, in the adult lung subjected to pneumonectomy (7), the pulmonary vasculature remodels by angiogenesis concomitant with ongoing alveolar growth. Moreover, a week’s exposure to hypoxia causes a major expansion in the numbers of acinar blood vessels in adult rats (8). However, this vascular response also accompanies an alveolar proliferative response.

These findings suggest that in the alveolar septum, pulmonary vascular angiogenesis is regulated by an epithelial-endothelial cross talk that maintains a balance between the alveolar and capillary surface areas. Thus, chronic blockade of endothelial receptors for VEGF (9) causes degeneration of both septal blood vessels and the alveolar wall, indicating the existence of trophic interdependence between alveoli and capillaries. This interdependence might be crucial in establishing the septal capillary density that optimally matches ventilation to perfusion.

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The paper by Alvarez et al. (1) in this issue of *AJP-Lung* also provides direct evidence for the angiogenesis potential of the pulmonary circulation. To assess endothelial replicative capabilities, these authors developed a proliferation assay for lung endothelial cells in which they grew individually sorted cells from large and small vessels of the rat lung in collagen-coated wells. Through this assay the authors provide evidence that lung microvascular endothelial cells, especially a subpopulation of these cells, proliferate at higher rates than their macrovascular counterparts. Although further studies are required to rule out the presence of bronchial endothelial cells in the subset of rapidly proliferating cells, the Alvarez data are good evidence that pulmonary microvascular endothelial cells possess an intrinsic capability for rapid proliferation.

Taking all of the data together, the emerging picture appears to be one in which the adult lung manages its requirements for neovascularization through angiogenic support from systemic vessels, whereas the intrinsic proliferative potential of the pulmonary vasculature is more or less held in check as long as alveoli are stable. Nevertheless, as discussed by Alvarez et al. (1), this intrinsic proliferative ability might be the critical mechanism that subserves repair of the pulmonary vasculature in lung injury. Endothelial directed knockout of the Forkhead box M1 (Fox M1) transcription factor, which is expressed in proliferating but not stable cells, reduces survival and increases lung permeability in septic mice (19). These findings indicate that proliferation-specific endothelial transcription factors are activated in lung injury, possibly to activate endothelial replication and repopulation in injured vascular segments.

The challenge facing us, then, is to recognize the signaling hierarchy that is brought into play by the lung’s need to increase blood supply in which proliferation signals are preferentially targeted to the systemic vasculature while being suppressed in the pulmonary vascular bed. A systematic understanding is required to clarify how these different signals are coordinated by the lung to bring about its characteristic neovascularization response.

**REFERENCES**


