Bronchopulmonary dysplasia (BPD) is one of the most common and significant medical complications associated with preterm birth, affecting 5000 to 10 000 babies annually. It was originally defined as a disorder occurring in infants who were ventilated for neonatal respiratory distress with the primary lung features being mucosal metaplasia of the airways, emphysema, widespread interstitial fibrosis, and remodeling of the small pulmonary arteries. Improvements in neonatal care, including antenatal steroids, surfactant therapy, better ventilator strategies, and improved nutritional support, although not reducing the incidence of the disease (the overall number of patients with BPD has increased), have led to the development of what is now called “the new BPD.” This so-called new BPD is characterized histopathologically primarily by an impairment of alveolar formation, which often leads to long-term global reductions in alveolar number and gas exchange surface area. This impairment of alveolar and vascular development is believed to contribute increased morbidity including the development of late cardiopulmonary disease, exercise intolerance, and impairment of alveolar and vascular development is believed to contribute increased morbidity including the development of late cardiopulmonary disease, exercise intolerance, and increased risk of asthma, pulmonary hypertension, and the development of chronic obstructive pulmonary disease in these infants as they grow into adulthood. Thus, therapies aimed at promoting lung alveolar and vascular growth in these infants may be highly beneficial in the prevention of the normal sequence of lung vascular development is disrupted, probably as a consequence of alterations in the normally complex signaling between the developing alveolar epithelium and the adjacent mesenchyme and pulmonary capillaries. As such, hyperoxic injury to the epithelium could disrupt these critical signaling pathways and disrupt angiogenesis. In addition, direct injury to the developing vasculature could disrupt angiogenesis, which may further impair the alveolarization process. Defining critical factors involved in lung angiogenesis and alveolarization is critical for the design of therapeutic interventions.

Vascular endothelial growth factor (VEGF) is a potent angiogenic growth factor whose importance in the developing lung is evidenced by its presence at the distal tips of the developing lung buds and its receptor, VEGFR-2 (KDR/flk-1) on the endothelium surrounding these developing airways. Exposure of the developing lung to hyperoxia in a number of animal models, including baboons, rats, and mice, decreases the expression of VEGF and/or its receptors and inhibits alveolar development. In addition, it has been shown that antagonism of angiogenesis and, in particular, VEGF, leads to vascular and alveolar simplification in the developing lung. Diminished expression of VEGFR-2 has also been identified as pivotal in the alveolarization process. Interestingly, overexpression of VEGF also leads to loss of integrity of the alveolar capillary membrane and alveolar simplification. The heparin sulfate–binding isoform of VEGF, VEGF188, an isoform whose expression increases significantly shortly before birth, appears especially important in the alveolarization process. Mice expressing only the diffusible VEGF120 isoform presented at birth with reduced peripheral air spaces and microvasculature with fewer air blood barriers. That VEGF is important not only in alveolar development but also in the maintenance of alveolar structure is supported by the occurrence of emphysema in adult rats treated with VEGF receptor inhibitors and in adult mice with lung-targeted VEGF inactivation. Collectively, these observations provide strong support for the hypothesis that VEGF-driven angiogenesis is crucial for normal alveolarization and that restoration of VEGF in situations characterized by decreased lung VEGF expression, if achieved in the right balance in the proper location, will enhance lung angiogenesis and thereby promote alveolarization.

In this issue of Circulation, Thebaud et al tested these hypotheses and present convincing evidence that lung-specific adenoviral (Ad) -mediated overexpression of VEGF promotes lung angiogenesis and stimulates alveolarization in a hyperoxia-induced neonatal rat model of BPD. Administration of Ad-VEGF by intratracheal injection allowed deliv-
other investigators have recently explored the possibility that transcription factors are necessary for normal fetal lung growth, normal capillary development and function in the setting of combined therapies likely will be necessary to re-establish were functionally less permeable. These studies suggest that therapy approach resulted in more mature capillaries that... factors with VEGF and VEGFR-2 in hypoxic neonatal models of hyalopoealveolariza-

Thus, the investigators in the present study provided iNO treatment after hypoxic exposure of neonatal rats not only increased overall growth but also improved distal lung growth despite persistent decreases in lung VEGF expres-

Perhaps even more important, the present study demonstrates the ability of lung-specific VEGF gene transfer to reverse established hypoxia-induced hyalopoealveolarization of the lung. Rescue experiments performed by administering recombinant Ad-VEGF beginning at day 21 of hypoxic exposure restored lung growth, which is perhaps surprising because it has been suggested that hypoxic exposure of neonatal rats produces permanent changes in lung structure. Recent studies with systemic VEGF administration also showed an improvement in alveolar structure during recovery from neonatal hypoxia.

These observations further support the possibility that interventions aimed at increasing lung growth are possible in established lung disease (ie, BPD).

It has been noted in other organ systems that treatment with VEGF alone can lead to the development of capillaries that are immature and are inherently leaky, probably because they lack a pericyte coating. Le Cras et al have described vessels of this type in the lungs of VEGF–overexpressing mice. Thus, the investigators in the present study provided angiopoietin-1 (Ang-1), a protein known to act in stabilizing nascent blood vessels, with VEGF. Using this strategy, they not only observed enhanced angiogenesis but also provided evidence by electron microscopy that this combined gene therapy approach resulted in more mature capillaries that were functionally less permeable. These studies suggest that combined therapies likely will be necessary to re-establish normal capillary development and function in the setting of neonatal lung injuries.

Given the fact that hypoxia and hypoxia-inducible transcription factors are necessary for normal fetal lung growth, other investigators have recently explored the possibility that stabilizing hypoxia-inducible factor-1α and 2α (HIF-1α, HIF-2α), which have important downstream targets including VEGF and NO, may lead to similar improvements in situations of interrupted postnatal lung development. In the vasculature, HIF regulates >500 genes, which are necessary for normal vascular growth and function. Studies in the fetal baboon model of bronchopulmonary dysplasia have demonstrated reductions in the lung expression of HIF-1α expression. Thus, it seems possible that preventing HIF degradation under hypoxic conditions could be beneficial. Prolyl-hydroxylase activity is necessary for HIF degradation under normoxic conditions. A variety of prolyl-hydroxylase inhibitors have been described recently. Asikainen et al examined the effect of a number of prolyl-hydroxylase inhibitors in lung tissue and cells and found that they could potently stabilize HIF even under hypoxic conditions. In addition, they found that these prolyl-hydroxylase inhibitors caused the release of VEGF into the culture media of human lung microvascular endothelial cells as well as A459 cells and showed that these changes were mediated, at least in part, through changes in VEGFR-2 receptor binding. Preliminary experiments in the premature baboon model of BPD with prolyl-hydroxylase inhibitors have been performed and have shown improvement in overall lung development and lung function. In addition, treatment of hyperoxic neonatal rats with the well-known HIF target erythropoietin was recently shown to improve alveolar structure, enhance vascularity, and decrease fibrosis.

In conclusion, it is becoming increasingly clear that the processes of alveolarization and lung capillary development are tightly linked. These processes are interrupted in the infant born prematurely and the consequent abnormalities on lung growth can have long-lasting effects on lung function. The studies reported by Thebaud and associates raise new possibilities for the treatment of infants with severe chronic lung disease. It seems possible that by augmenting or restoring vascular growth, overall lung growth and ultimately lung function can be restored. Extreme caution must be exercised, however, before extending findings from preclinical studies in rodent models to the treatment of human disease. The hypoxia-exposed neonatal rodent lung displays only the alveolar simplification but not the interstitial fibrosis and severe inflammatory response seen in human infants dying from BPD. Interestingly, a recent study in infants with BPD suggests that the changes in lung architecture are not simply a result of decreased angiogenesis. In fact, there is evidence in some patients that overall lung capillary density is increased. Thus, attention must be given to the timing of angiogenic therapy to avoid potentially deleterious effects, such as stimulating abnormal vascular growth. It is possible that stimulating angiogenesis at the wrong time or in the wrong compartment could contribute to rather than ameliorate lung injury. Large systemic (bronchial) collaterals have been observed in infants with BPD. Angiogenic therapy could stimulate the growth of these vessels, which have been considered to contribute to the morbidity of the disease. Furthermore, abnormal vascularization could provide a conduit for the continued delivery of inflammatory cells or progenitor cells, which may act in maladaptive ways, causing further fibrosis. The present findings, however, do suggest that we must continue to investigate the possibility that someday we will be able to restore normal lung growth and thus ameliorate one of the major problems of premature birth.

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References


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