Lung Development and Susceptibility to Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease with emphysema has been considered to be an accelerated involutorial disease of aging smokers. However, because only a proportion (~15%) of smokers develop chronic obstructive pulmonary disease with emphysema, clearly genetic susceptibility must play a significant part in determining both the age of onset and the rapidity of decline in lung function. In mice, interference with key genes, either by null mutation, hypomorphism, or gain or loss of function, results in phenotypes comprising either neonatal lethal respiratory distress if the structural effect is severe, or reduced alveolarization and/or early-onset emphysema if the effect is milder. Likewise, null mutants that interfere with matrix assembly and/or integrity, such as elastin, lysyl oxidase, or fibrillin, also result in alveolar dysplasia. Importantly, null mutation of Smad3, which encodes a receptor-activated Smad in the transforming growth factor-β signaling pathway, results in a more subtle failure to correctly organize the alveolar matrix, which is in turn antecedent to early-onset emphysema mediated by matrix metalloproteinase-9. Furthermore, exposure to sidestream smoke profoundly exacerbates and accelerates alveolar destruction, leading to more severe early-onset emphysema in young Smad3-null mice (unpublished data). Interestingly, polymorphisms in the fibrillin, transforming growth factor-β type II receptor, and matrix metalloproteinase-9 genes have been described in humans with emphysema. Thus, dysplastic or degraded matrix cannot provide the structural niche for alveolar stem/progenitor cells to assume the correct phenotype and/or repair the alveolar cell lineage niche. The hope is that providing the correct exogenous signals can coax them into doing so.

Keywords: lung development; disease susceptibility genes; chronic obstructive pulmonary disease

LUNG DEVELOPMENT

The lung arises from the floor of the primitive forugut as the laryngotracheal groove, at around 4- to 6-wk gestation in humans and embryonic day (E) 10 in mice (Figure 1). The proximal portion of this primitive structure gives rise to the larynx and trachea, which become separated from the esophagus, whereas progenitor cells located at the distal portion of the primitive trachea give rise to the left and right main-stem bronchi. Branching morphogenesis of the left and right bronchi to form specific lobar, segmental, and lobular branches extends through the canalicular stage of lung development up to about 20-wk gestation in humans (Figure 2). The first 16 of these 23 airway generations are stereospecific in humans, with the remainder being fractal in geometry, but with a distinct proximal–distal pattern of diameter and epithelial differentiation that are genetically hard-wired (Figures 3–5). Alveolarization begins at about 20 wk in humans and continues at least up to 7 yr of age, giving rise to an alveolar gas diffusion surface 70 m² in area by 1-μm thick. This enormous surface is closely apposed to an alveolar capillary network capable of accommodating a blood flow between 5 L/min at rest and 25 L/min at maximal oxygen consumption. The entire developmental process of the lung is orchestrated by finely integrated and mutually regulated networks of transcriptional factors, growth factors, matrix components, and physical forces. In utero, the lung is a hydraulic, fluid-filled system. Secretion of fluid into the airway lumen is osmotically driven by chloride channels. The larynx maintains an intraluminal hydraulic pressure of approximately 1.5 cm H₂O. Excess fluid drainage during fetal life results in hypoplasia of the lung. Conversely, obstruction of the trachea in embryonic lung in culture can result in a doubling of the rate of airway branching. Moreover, fluctuations in intraluminal pressure caused by coordinated peristaltic contractions of airway smooth muscle have recently been shown to play an important role in branching morphogenesis. After cord clamping and a rush of catecholamines at birth, the lung lumen dries out and rapidly switches to air breathing. Clearance of lung intraluminal liquid is mediated by activation of sodium transport. Null mutation of sodium transporter channel genes (α ENaC) is neonatal lethal because it abrogates this fluid uptake (1–4). "Erection" of alveolar septa is relatively poorly understood. Nevertheless, correct organization of elastin matrix niche is important, as is remodeling of the alveolar capillary network. This suggests that vascular hydraulic perfusion pressure may play a key role in the emergence of septal structures into the alveolar space. This concept is further supported by a requirement for vascular endothelial growth factor secretion by the alveolar epithelium to maintain vascular integrity and hence correct epithelial branching as well as alveolar morphogenesis (5, 6).

FACTORS THAT ADVERSELY IMPACT LUNG DEVELOPMENT

Factors that adversely impact the developing lung, including human prematurity, oxygen exposure, corticosteroid exposure, incorrect amounts of growth factor (platelet-derived growth factor, fibroblast growth factor [FGF], vascular endothelial growth factor, transforming growth factor [TGF]-β) signaling, abnormal regulation, or injury of the pulmonary capillary vasculature, all result in hypoplasia of the alveolar epithelial surface, with a resulting deficiency in gas transport, particularly during exercise. For example, survivors of human prematurity with bronchopulmonary dysplasia will desaturate on maximal exercise during childhood, and some are now entering young adulthood with increasingly severe gas diffusion problems.

AGING AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

At the other end of the developmental spectrum, namely during aging, progressive involution of alveolar gas diffusion capacity...
occurs, especially over the last decades of life. This involution may be accelerated by exposure to adverse environmental factors, such as tobacco smoke, smog, industrial pollutants, toxic inhalants, infectious agents, and so forth. In industrialized societies where these risk factors are present, there is an epidemic of pulmonary failure due to chronic obstructive pulmonary disease (COPD), which is now the fourth leading cause of adult death in the United States.

SUSCEPTIBILITY FACTORS AND COPD

COPD with emphysema has hitherto been considered to be an accelerated, involutional disease of aging smokers. However, because only a certain proportion (~ 15%) of smokers develop COPD with emphysema, genetic susceptibility clearly must play a significant part. Recently, we have begun to wonder whether developmental issues may underlie at least some susceptibility to apparently adult-onset chronic lung disease. Certainly, the increasing numbers of survivors of human prematurity may be at risk. However, there may be other more subtle developmental genetic issues of concern.

DEVELOPMENTAL RISK FACTORS AND LUNG DISEASE

In mice, interference with many key genes, either by null mutation, hypomorphism, or gain or loss of function, results in final
common phenotypes comprising either neonatal lethal respiratory distress if the structural effect is severe, or reduced alveolarization and early-onset emphysema if the effect is milder. For example, Fgf10- as well as Fgfr2b-null mutations completely abrogate lung branching morphogenesis distal to the carina, whereas hypomorphic or ectopic FGF signaling results in neonatal-lethal alveolar dysplasia. This demonstrates that correct FGF signaling is absolutely required for lung morphogenesis distal to the carina, as well as for correct progress of all subsequent stages of lung development up to and including alveolarization (1).

CORRECT FORMATION OF THE ALVEOLAR NICHE AND ELASTIC INTERDEPENDENCE

In the lung, normal deposition and arrangement of elastin fibers is particularly important in the formation and maintenance of
alveolar crests. For example, in young mice with the Elastin-null mutation, alveolar crests fail to form (7). Null mutation of lysyl oxidase prevents correct elastin cross-linking and, hence, alveolarization is incomplete (8). Similarly, in mice with the Pdgfa-null mutation, alveolar myofibroblasts fail to differentiate and produce elastin; hence, alveolar crests also fail to form (9). Excessive, dysmorphic elastin is laid down, which also disrupts the formation of alveolar crests (10). On the other end of the developmental spectrum, failure to protect elastin from proteolytic degradation in α1-antitrypsin deficiency (11), or from excessive destruction of elastin, mediated by neutrophil elastase induced by chronic cigarette smoke exposure, results in the disease termed “emphysema,” which is characterized by destruction of the alveolar walls. Elastic interdependence of the lung is an important concept in respiratory physiology, which accounts for orderly elastic recoil of the lungs during passive expiration. At the alveolar level, elastic interdependence is mediated by the correct expression, cross-linking, and orientation of elastin and collagen fibers. Thus, absence of correctly cross-linked and oriented elastin containing matrix predisposes to failure of correct establishment of elastic interdependence and alveolarization, whereas excessive degradation of elastin containing matrix underlies loss of elastic interdependence and alveolar degeneration (Figure 6).

TGF-β SIGNALING PATHWAY AND MATRIX METALLOPROTEINASES AS RISK FACTORS FOR EARLY-ONSET LUNG DISEASE

Null mutation of Smad3, which is a key receptor-activated Smad in the TGF-β signaling pathway, results initially in a rather subtle failure of correct organization of the matrix, which in turn is an antecedent of the subsequent, early-onset pulmonary emphysema (12). This early-onset emphysema in the Smad3-null mutants is also associated with activation of excessive matrix metalloproteinase (MMP) activity (Figure 7). Thus, correct organization of the matrix during alveolarization may protect against...
subsequent proteolytic degradation and deterioration of the matrix, with subsequent loss of functional alveolar gas diffusion surface. We have also recently found that exposure to side-stream smoke profoundly exacerbates and accelerates alveolar destruction in young Smad3-null mice (unpublished data).

Although these results provide further support for the concept that failure of correct matrix organization may predispose to certain serious degenerative diseases, conversely, correct matrix organization may be protective against these same degenerative diseases. Interestingly, polymorphisms in the fibrillin, latent TGF-β binding protein-4 in the TGF-β pathway, and MMP genes have been described in humans with emphysema (13–15). Also, mutations in endoglin, a proteoglycan that modulates signaling functions in the TGF-β pathway, are responsible for pulmonary telangiectasia (16). In contrast, excessive expression of the bone morphogenetic protein 4 (BMP4) growth factor inhibitor Gremlin has recently been described in certain specific forms of pulmonary fibrosis. Therefore, inhibitors of the inhibitors might also be worth investigating.

PROGENITOR CELLS AND THE FUTURE

One quite novel way of interpreting these seemingly disparate results is that dysplastic or degraded matrix can provide neither the structural niche nor the environmental cues for alveolar stem/progenitor cells to assume the correct phenotype and/or repair the correct alveolar cell lineage matrix niche. For example, up- or down-dysregulation at several critical points in the TGF-β pathway results in pulmonary pathobiological outcomes that can be interpreted in this light: null mutation of TGF-β1 results in lethal lung inflammation; excessive TGF-β1 expression results in alveolar hypoplasia (bronchopulmonary dysplasia) in the neonate versus fibrosis in the adult. The hope is that protecting the structural niche nor the environmental cues for alveolar progenitor cell population with small, soluble molecules and/or providing the correct exogenous signals can coax alveolar progenitor cells into maintaining or repairing the alveolar gas diffusion surface (17, 18).

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